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TABLE OF CONTENTS ON PAGE 6

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# CONTENTS FOR JULY, 1942

## Original Communications

|  |     |
|--|-----|
| The Causes of Fetal and Neonatal Mortality. D. Anthony D'Esopo, M.D., and Andrew Anthony Marchetti, M.D., New York, N. Y. ....   | 1   |
| The Clinical Similarity of Corpus Luteum Cyst and Ectopic Pregnancy. S. Leon Israel, M.D., Philadelphia, Pa. ....  | 22  |
| Renal and Ureteral Calculi in Pregnancy. Rupert E. Arnell, M.D., F.A.C.S., and Paul L. Getzoff, B.S., M.D., New Orleans, La. ....  | 34  |
| Toxic Manifestations in the Newborn Infant Following Placental Transmission of Sulfanilamide. Arthur M. Ginzler, M.D., and Charles Chesner, M.D., New York, N. Y. ....   | 46  |
| Cyclical Estrogen Therapy. Allan Palmer, M.D., San Francisco, Calif. ....  | 56  |
| Glomerular Filtration and Renal Blood Flow in "Normal" Patients Following Toxemias of Pregnancy. L. V. Dill, M.D., C. E. Isenhour, M.A., J. F. Cadden, M.A., and C. E. Robinson, M.D., New York, N. Y. ....    | 66  |
| The Routine Use of Bicycle Exercises for the Prophylaxis of Postoperative Thrombophlebitis. Joseph M. Krebs, M.D., St. Louis, Mo. ....   | 73  |
| The Identification of Fetal Squamas and the Diagnosis of Ruptured Membranes by Vaginal Smear. George A. Bourgeois, M.D., Jersey City, N. J. ....   | 80  |
| Comparative Local Tissue Reaction and Styptic Action of Sulfanilamide. Clayton T. Beecham, B.S., M.D., and Rupert Friday, A.B., M.D., Philadelphia, Pa. ....   | 88  |
| Macrocytic Hyperchromic Anemia of Pregnancy. Mark Daniel, M.D., and Max Antis, M.D., New York, N. Y. ....  | 93  |
| Use of Mercurochrome to Avoid Postoperative Catheterizations. C. Gordon Johnson, M.D., F.A.C.S., New Orleans, La. ....   | 98  |
| Treatment of Hyperemesis Gravidarum With Intramuscular Injections of Husband's Blood. Wendell L. Hughes, M.D., F.A.C.S., and Arthur C. Martin, M.D., F.A.C.S., Hempstead, N. Y. ....                           | 103 |
| The Use of Estrogens in the Treatment of Leucoplakia, Kraurosis, and Senile Vaginitis. C. L. Buxton, M.D., Med. Sc.D., New York, N. Y. ....  | 109 |
| The Use of Methyl Testosterone for the Relief of Breast Engorgement in the Puerperium. S. Duckman, M.D., and T. R. Turino, M.D., Brooklyn, N. Y. ....  | 112 |
| The Relation Between Uterine Activity and Reactivity to Posterior Pituitary Extract During Pregnancy. Douglas P. Murphy, M.D., Philadelphia, Pa. ....  | 117 |
| Blood Transfusion Reaction Due to Intra-Group Incompatibility. Philip E. Crooks, M.D., New York, N. Y. ....  | 121 |
| Immediate Post-Partum Repair of Old Perineal Lacerations. Edward G. Waters, M.D., F.A.C.S., Jersey City, N. J., Eakle W. Cartwright, M.D., Pasadena, Calif., and J. Edward Lynch, M.D., Philadelphia, Pa. .... | 124 |
| Ruptured Ovarian Pregnancy. Morris Courtiss, B.S., M.D., Boston, Mass. ....  | 128 |
| Unusual Coexistence of Granulosa Cell Tumor and Ovarian Teratoma Containing Thyroid Tissue. Nelson A. Murray, M.D., Malcolm B. Dockerty, M.D., and John deJ. Pemberton, M.D., Rochester, Minn. ....            | 134 |
| Bilateral Brenner Tumor of the Ovary. Augustin R. Peale, M.D., Philadelphia, Pa. ....  | 138 |
| Sarcoma Botryoides of the Cervix. Henry S. Fischer, B.S., M.D., F.A.C.S., and A. R. Kantrowitz, M.D., Brooklyn, N. Y. ....   | 141 |
| Tuberculosis of the Vulva. Woolfolk Barrow, M.D., and E. S. Maxwell, M.D., Lexington, Ky. ....   | 145 |
| An Apparatus for Resuscitation of Newborn Infants. Leonard H. Biskind, M.D., and Eduard Eichner, M.D., Cleveland, Ohio ....  | 147 |
| Method for Correlating Data From Menstrual Cycles of Different Lengths. Samuel R. M. Reynolds, Ph.D., Baltimore, Md. ....  | 151 |
| An Improved Vehicle for Medication of the Vagina. George A. Williams, M.D., Atlanta, Ga. ....  | 153 |

(Continued on page 8)



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## CONTENTS (Continued from page 6)

## Special Articles

|   |     |
|---|-----|
| Contributions of Studies on Primate Animals to Gynecologic Thought. Carl G. Hartman, Ph.D., Urbana, Ill. .... | 156 |
| Prepared Parents—The Core of Creative Family Living. Hazel Corbin, R.N., New York, N. Y. ....                 | 166 |

## Society Transactions

|   |     |
|---|-----|
| Chicago Gynecological Society, Meeting of January 16, 1942 .....                    | 171 |
| Washington Gynecological Society, Meeting of November 22, 1941 .....                | 171 |
| Meeting of January 24, 1942 .....   | 171 |
| Pittsburgh Obstetrical and Gynecological Society, Meeting of February 2, 1942 ..... | 171 |

## Department of Reviews and Abstracts

|  |     |
|--|-----|
| Selected Abstracts—Endometriosis ..... | 172 |
| Myoma .....                            | 179 |

## Correspondence

|                      |     |
|----------------------|-----|
| Correspondence ..... | 180 |
|----------------------|-----|

## Roster

|  |     |
|--|-----|
| Roster of American Obstetrical and Gynecological Societies ..... | 181 |
|--|-----|

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## Original Communications

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### THE CAUSES OF FETAL AND NEONATAL MORTALITY\*

D. ANTHONY D'ESOP, M.D., AND ANDREW ANTHONY MARCHETTI, M.D.,  
NEW YORK, N. Y.

*(From the Department of Obstetrics and Gynecology, Sloane Hospital for Women  
and College of Physicians and Surgeons, Columbia University, and the  
Department of Obstetrics and Gynecology, Lying-in Hospital)*

THE study of the causes of fetal mortality should be an increasingly important problem, for only in this way will it be possible to devise methods which will offer sufficient safety to the child to give us courage to avoid the tempting but less safe cesarean section.

With an ever-increasing emphasis on the importance of delivering a normal healthy child for each planned pregnancy, the obstetrician frequently finds himself in the position of recommending cesarean section on purely fetal indications. While this method of delivery usually offers the easiest way out of a difficult situation and frequently improves the chances of fetal survival, we cannot overlook the discomfoting fact that the risk to the mother is much greater under these circumstances than when the delivery is effected through the vagina. It seems logical, therefore, to increase our efforts in the study of the causes of fetal deaths, with the hopeful outlook that the pelvic delivery, which unquestionably offers maximum safety to the mother, may be made increasingly safe for the child. Only in this way will it be possible further to lower *both* the fetal and maternal mortality. A high fetal mortality rate cannot be

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\*Presented at a meeting of the New York Obstetrical Society, October 14, 1941.

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."



combated entirely with a high cesarean section rate, for it may be shown readily from our figures that, even if a cesarean section were done in every patient that came to the labor room, there still would be a minimum fetal loss of 2.3 per cent, due to causes which are in no way related to the accidents of labor and which could not be prevented by the operation. Obviously then, an increasing cesarean section rate will have the effect of giving diminishing returns in terms of live births while the maternal mortality would unquestionably rise sharply or, to put it in another way, an increasing cesarean section rate reaches a point where it costs too many mothers for the prospect of saving a proportionately smaller number of babies.

It was with these general ideas in mind that this study was contemplated. It represents a critical clinical and pathologic review of 1,000 consecutive fetal deaths occurring at the New York Lying-in Hospital and the Sloane Hospital for Women. The study covers a period of six years from 1935 to 1940, inclusive. The data from both services have been combined and presented in that form.

There are no striking differences in the nature of the material handled, the organization of staffs, or the physical equipment of these services. In most respects, the figures obtained were entirely comparable and seem suitable to present in a combined form.

Among the 1,000 deaths reviewed, only 16 occurred among unregistered cases. There was a combined autopsy rate of 89.3 per cent. Thus it is seen that in the vast majority of cases there were both complete clinical and pathologic data available for study.

Notwithstanding such complete clinical and anatomic data, it is not always a simple matter to evaluate the factors that are concerned with a fetal death. Even when the anatomic findings of a carefully performed post-mortem examination are known and these are correlated with the events which occurred during labor, it may be difficult to classify the death with certainty. The multiplicity of factors involved in a single case and the various degrees of emphasis placed upon them may lead different observers to reach different conclusions in ascribing primary and secondary causes of death. A good example is the frequently seen premature baby weighing about 2,000 Gm. with a small amount of subdural hemorrhage. The difficulty of ascribing primary and secondary causes of death in such a case becomes obvious at once. If the weight of the fetus were changed from 2,000 Gm. to 1,000 Gm., then prematurity as the primary cause with birth trauma as a secondary cause would be in more general agreement. There are other factors which make for difficulty. These involve the actual interpretation of post-mortem findings. Neonatal pathology in many instances lacks the confirmatory data of the experimental pathologist, so that the inter-

pretation of the lesions we see are not always clear. To mention one such lesion we may refer again to the intracranial hemorrhages found in the premature infant. Frequently these occur as small subarachnoid or intraventricular hemorrhages with no evidence of injury to the dural supporting system, while the lungs, pleura, pericardium, thymus, adrenals, and other viscera show the ruptured capillaries so characteristic of asphyxia. In such a case, it is a matter of individual interpretation to ascribe the intracranial findings either to birth injury on the one hand or to asphyxia on the other. What is the significance of hemorrhage into the lung? Is it related to the hemorrhagic lesions of the newborn or does it represent evidence of intrauterine asphyxia? What is the significance of masses of amniotic cells in the lungs? Are they evidence of asphyxia followed by aspiration of amniotic fluid and cells or is their presence physiologic, as a part of the so-called tidal flow of amniotic fluid? What is the relationship of congenital pneumonia to asphyxia? Does pneumonia follow after asphyxia, which causes the child to aspirate large quantities of bacteria and pus cells from an infected amniotic sac, or do these organisms gain access to the lungs by some other mechanism? It is obvious, therefore, that, while in a majority of cases the primary cause of death may be ascribed with certainty, there are a considerable number in which the final classification becomes an opinion based on all the clinical and anatomic facts available and its accuracy depends largely upon the completeness of these facts and the judgment and clinical-pathologic experience of the observer.

At the very beginning of the study we found it necessary to reach some agreement on the classification of the premature infant, because the respective institutions followed different practices in this respect. Hence, we reclassified all the fetal deaths according to the classification of Scammon (Table I).

TABLE I

|   |               |
|---|---------------|
| Previaible prematures   | 92            |
| (Must satisfy any two of the following criteria)                        |               |
| From 500 to 999 Gm. in weight   |               |
| From 28 to 35 cm. in length   |               |
| From 22nd to 28th week  |               |
| Viable prematures   | 350           |
| (Must satisfy any two of the following criteria)                        |               |
| From 1,000 to 2,499 Gm. in weight                                       |               |
| From 35.1 to 47 cm. in length   |               |
| From 29th to end of 37th week   |               |
| Term  | 558           |
| Total   | <hr/> 1,000   |
| Total deliveries  | 25,823        |
| Total fetal and neonatal deaths   | 1,000         |
| Gross fetal and neonatal mortality rate                                 | 3.87 per cent |
| Fetal and neonatal mortality rate exclusive<br>of previaible prematures | 3.52 per cent |

Some question might be raised about the inclusion of the previable premature infants in this study, since the mortality rate in this group is very nearly 100 per cent. There are several reasons why it seems desirable to include them in any study of stillbirths. First, these tiny babies occasionally live, and for this reason we should attempt to discover the causes of death in the others with the hope that more and more of them may be salvaged. Second, these infants may be studied by routine pathologic methods. To consider them as abortions rather than stillbirths tends toward their disposal along with other abortions in which routine pathologic techniques are not applicable. In the third place, they are frequently associated with maternal disease which necessitates an interruption of pregnancy. By adding them to the total group we obtain a more complete picture of the relationship of maternal disease to fetal deaths.

In Table I we note that there were 25,823 deliveries at both hospitals during the period covered by this study, resulting in a gross fetal mortality rate of 3.87 per cent. If the previable prematures are excluded, the rate becomes 3.52 per cent. On the basis of live births the rates are 4.03 per cent if the previable prematures are included and 3.66 per cent when they are excluded. The premature infants account for 44.2 per cent of the total number of deaths.

The causes of death in the entire group are shown in Table II.

TABLE II. DISTRIBUTION OF CAUSES IN 1,000 CASES OF FETAL AND NEONATAL DEATHS

| CAUSES                         | NUMBER OF CASES |
|--------------------------------|-----------------|
| Asphyxia                       | 198             |
| Prematurity (primary)          | 185             |
| Congenital abnormalities       | 141             |
| Maceration, cause unknown      | 130             |
| Birth injury                   | 115             |
| Congenital pneumonia           | 58              |
| Maceration and toxemia         | 52              |
| None                           | 30              |
| Erythroblastosis               | 28              |
| Hemorrhagic disease of newborn | 21              |
| Septicemia                     | 18              |
| Congenital syphilis            | 6               |
| Maceration and diabetes        | 5               |
| Diarrhea newborn               | 4               |
| Aspiration of food             | 3               |
| Perforated ulcer ileum         | 1               |
| Gangrene of colon              | 1               |
| Intestinal obstruction         | 1               |
| Multiple abscesses of liver    | 1               |
| Adrenal hemorrhage             | 1               |
| Toxoplasmosis                  | 1               |

Attention is called to the fact that these are listed as primary causes only. While it is obvious that in many instances there were multiple

causes of death, it seemed that a grouping according to combinations of primary and secondary causes would be cumbersome to the point of being valueless. Each case was carefully studied from both a clinical and a pathologic viewpoint, as previously stated, and an attempt was made to ascertain the most important cause of death.

Prematurity appears as the cause of death in 185 cases while Table I shows that 442 cases were classified in the premature group. The difference between these two figures (257), therefore represents the number of premature infants that died of causes that were more significant than their premature state and for that reason were classified under those causes. It follows, then, that a relatively large number of premature infants might have lived if they had not been the victims of some other pathologic conditions.

It is noteworthy that of the causes of death those which are more directly related to labor, namely: asphyxia (19.8 per cent), birth injury (11.5 per cent), and pneumonia (5.8 per cent), appear in that order.

A relatively large number of deaths (13 per cent) occurred before the onset of labor without known cause. These fetuses were born in a macerated state, and in the absence of any known cause are a distinct challenge to the research worker in this field. Our knowledge about this group is limited because the poor state of preservation of all cell structure makes post-mortem studies valueless. It will be of interest to follow the work that is being done with the Rh factor to see if deaths of this nature may be explained on that basis.

TABLE III. RELATIONSHIP OF RACE TO FETAL AND NEONATAL MORTALITY

|       | TOTAL NO. DELIVERED | NO. OF DEATHS | PERCENTAGE RATE |
|-------|---------------------|---------------|-----------------|
| White | 23,729              | 868           | 3.65            |
| Negro | 2,094               | 132           | 6.30            |

TABLE III, A. CAUSES OF DEATH AMONG WHITES AND NEGROES

| CAUSES                         | INCIDENCE AMONG TOTAL WHITES (PER CENT) | INCIDENCE AMONG TOTAL NEGROES (PER CENT) |
|--------------------------------|---|--|
| Asphyxia                       | 19.0                                    | 25.0                                     |
| Prematurity                    | 17.7                                    | 23.5                                     |
| Congenital malformations       | 14.7                                    | 9.8                                      |
| Maceration, cause unknown      | 13.6                                    | 9.0                                      |
| Birth injury                   | 11.7                                    | 9.8                                      |
| Maceration, due to toxemia     | 4.9                                     | 6.8                                      |
| Erythroblastosis               | 3.1                                     | 0.8                                      |
| Hemorrhagic disease of newborn | 1.9                                     | 3.0                                      |

TABLE IV. RELATIONSHIP OF PARITY TO FETAL AND NEONATAL MORTALITY

|            | TOTAL NO. DELIVERED | TOTAL NO. OF DEATHS | MORTALITY RATE |
|------------|---------------------|---------------------|----------------|
| Primiparas | 13,241              | 509                 | 3.84           |
| Multiparas | 12,582              | 491                 | 3.90           |

Maternal disease directly accounted for 6.3 per cent of all fetal deaths. This figure, however, does not completely express the importance of maternal disease in the problem since, in at least an additional 55 cases, maternal disease was indirectly responsible for a premature labor which in turn resulted in a stillbirth or neonatal death. It may be stated, therefore, that 11.8 per cent of the fetal deaths were directly or indirectly the result of maternal disease. Congenital syphilis accounted for only 0.6 per cent of the deaths. This figure is in marked contrast to those found in older reports when syphilis was among the most important causes.

The fetal mortality rate among the whites and Negroes as noted in Table III shows a definitely higher rate among the latter. The causes

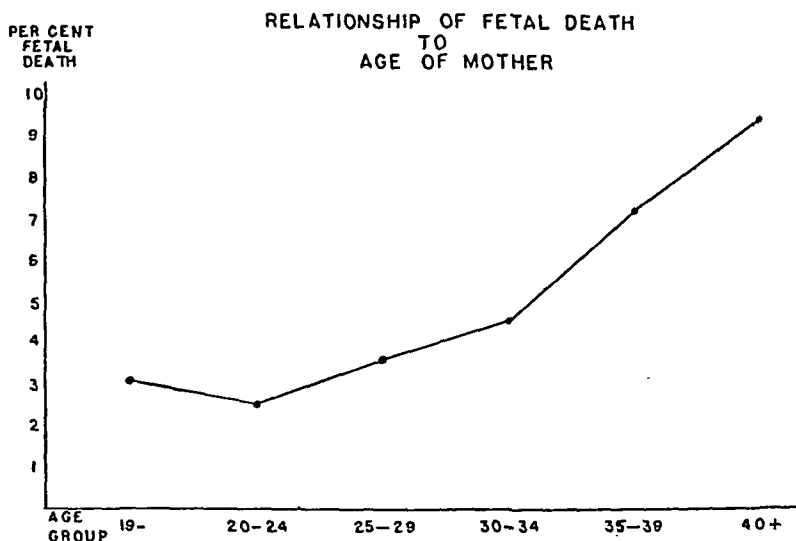


Fig. 1.

of death were studied separately and those conditions which showed differences of more than 1 per cent are recorded in Table IIIA. The higher fetal mortality rate among the Negroes was due mainly to a higher incidence of prematurity and asphyxia. They also showed a slightly higher incidence of deaths due to toxemia and hemorrhagic disease of the newborn. Among the whites, on the other hand, there was a greater fetal death rate due to congenital malformations, maceration of unknown cause and erythroblastosis.

It was of interest to note (Table IV) that the fetal death rate among multiparas and primiparas is practically identical. Apparently the larger number of deaths due to dystocia among primiparas is completely balanced in the multiparas by the higher incidence of deaths due to the accidents of labor.

The relationship of the age of the patient to the proportion of living and dead infants delivered at each age level is shown graphically in Fig. 1, from which we may conclude that the incidence of fetal deaths was lowest among the women between 20 and 24 years of age and highest in women that were 40 years old or over. There is a gradual rise in fetal mortality rate as the woman advances beyond age 30, in spite of the greater latitude in operative interference aimed toward saving the fetus in these cases.

We next studied the relationship of the duration of labor to fetal mortality (Table V) and noted that labors under three hours and those

TABLE V. RELATIONSHIP OF THE DURATION OF LABOR TO FETAL AND NEONATAL MORTALITY

|                     | LESS<br>THAN 3<br>HOURS | 3-5   | 6-11  | 12-17 | 18-23 | 24-29 | MORE<br>THAN 30<br>HOURS |
|---------------------|-------------------------|-------|-------|-------|-------|-------|--------------------------|
| Total No. delivered | 1,216                   | 4,182 | 7,993 | 5,136 | 2,774 | 1,115 | 2,062                    |
| No. of deaths       | 81                      | 140   | 237   | 170   | 82    | 55    | 181                      |
| Percentage rate     | 6.66                    | 3.34  | 2.96  | 3.40  | 2.95  | 3.88  | 8.77                     |

that exceed thirty hours show distinctly higher mortality rates. The mortality rate for labors that exceed thirty hours more than doubles, and for this reason it would seem reasonable to advocate consultation in all such cases unless the delivery is imminent.

TABLE VI. RELATIONSHIP OF FETAL AND NEONATAL MORTALITY TO METHOD OF DELIVERY

| METHOD OF DELIVERY  | TOTAL<br>DELIVERED | TOTAL<br>DEATHS | PERCENTAGE<br>RATE |
|---------------------|--------------------|-----------------|--------------------|
| Spontaneous vertex  | 19,916             | 529             | 2.6                |
| Low forceps         | 2,672              | 89              | 3.3                |
| Midforceps          | 1,011              | 65              | 6.4                |
| Cesarean section    | 782                | 57              | 7.3                |
| Breech delivery     | 1,084              | 152             | 14.0               |
| Version, extraction | 182                | 42              | 23.1               |
| High forceps        | 29                 | 12              | 41.4               |
| Craniotomy          | 38                 | 38              | 100.0              |
| Miscellaneous       | -----              | 16              | ----               |

The methods by which the infants in this study were delivered is shown in Table VI. From the data, we note:

1. The lowest mortality rate (2.6 per cent) occurred in the spontaneous vertex deliveries. The low forceps group was slightly higher (3.3 per cent). This need not disconcert the advocates of the prophylactic low forceps since in both institutions the low forceps operation is done on definite indications only and for that reason our mortality rate in low forceps deliveries is not comparable with their figures.
2. A high gross fetal mortality rate in those patients delivered by cesarean section (7.3 per cent).
3. An extremely high mortality rate in the high forceps operation (41.4 per cent).
4. Almost one-fourth of the infants delivered by version extraction die. While this is an uncorrected figure, it appears unusually high and is explained largely by the fact that forceps are distinctly preferred to the version operation in both institutions. For this reason, version extraction is reserved for the more difficult cases in which forceps cannot be applied. Again this rate is

not comparable with the figures obtained by those who advocate wide indications for the version-extraction operation.

The gross infantile mortality in breech deliveries (14 per cent) warrants inquiry into the causes of death in these cases. This is shown in Table VII. Here we note that prematurity, congenital abnormalities,

TABLE VII. RELATIONSHIP OF BREECH DELIVERY TO CAUSES OF FETAL AND NEONATAL DEATH

| CAUSES                              | NO. CASES<br>(152) | DEATH RATE<br>(PER CENT) |
|-------------------------------------|--------------------|--------------------------|
| Prematurity                         | 35                 | 23.0                     |
| Asphyxia                            | 28                 | 18.4                     |
| Congenital abnormalities            | 26                 | 17.1                     |
| Maceration                          | 26                 | 17.1                     |
| Birth injury                        | 18                 | 11.8                     |
| Congenital pneumonia and septicemia | 9                  | 5.9                      |
| Congenital syphilis                 | 2                  | 1.3                      |
| Erythroblastosis                    | 2                  | 1.3                      |
| Hemorrhagic disease                 | 2                  | 1.3                      |
| Liver abscesses                     | 1                  | 0.7                      |
| Aspiration of food                  | 1                  | 0.7                      |
| Diarrhea newborn                    | 1                  | 0.7                      |
| None                                | 1                  | 0.7                      |
|                                     | 152                | 100.0                    |

and unexplained ante-partum deaths accounted for 47.2 per cent of the breech mortality. The causes of deaths that are more directly related to labor and to a large extent preventable, namely, asphyxia, birth injury, and pneumonia, accounted for 36.1 per cent of the breech deaths. In this latter group of causes asphyxia rather than birth injury ranked first.

A detailed study of the causes of fetal death in midforceps deliveries (Table VIII) showed that 46.1 per cent were due to birth injuries. The

TABLE VIII. RELATIONSHIP OF MIDFORCEPS DELIVERY TO CAUSES OF FETAL AND NEONATAL DEATH

| CAUSES                      | NO. CASES<br>(65) | DEATH RATE<br>(PER CENT) |
|-----------------------------|-------------------|--------------------------|
| Birth injury                | 30                | 46.1                     |
| Congenital pneumonia        | 12                | 18.5                     |
| Asphyxia                    | 9                 | 13.9                     |
| Congenital abnormalities    | 4                 | 6.2                      |
| Hemorrhagic disease newborn | 3                 | 4.6                      |
| Maceration                  | 2                 | 3.1                      |
| No cause                    | 2                 | 3.1                      |
| Prematurity                 | 1                 | 1.5                      |
| Erythroblastosis            | 1                 | 1.5                      |
| Gangrene colon              | 1                 | 1.5                      |
|                             | 65                | 100.0                    |

30 cases that make up this midforceps birth injury group would in themselves provide enough material for an interesting report. Categorically it may be stated that at least four types of errors were made in these cases, viz.:

1. Forceps were applied in the face of disproportion when a cesarean section should have been done.

2. Traction and rotation was not ideally adapted to the architecture of the pelvis.
3. Forceps were applied too late, after the fetus had been comprised by an excessively long labor which resulted in asphyxia or congenital pneumonia.
4. Traction was too rapid in an attempt to save the child from asphyxia.

As previously noted, the gross infantile mortality rate in cesarean sections was 7 per cent. This simply reflects the large number of cesarean sections that were done because of maternal complications irrespective of the fetal prognosis. A finding that caused some surprise was the fact that 5 of the 57 infants in this group died of a birth injury (Table IX).

TABLE IX. RELATIONSHIP OF CESAREAN SECTION AND THE INDICATIONS TO THE CAUSES OF FETAL DEATH

| INDICATIONS                      | TERM | PRE-MATURE | TOTAL | FETAL DEATHS           |     |
|----------------------------------|------|------------|-------|------------------------|-----|
|                                  |      |            |       | CAUSE                  | NO. |
| Premature separation of placenta | 10   | 14         | 24    | Asphyxia               | 20  |
|                                  |      |            |       | Congenital abnormality | 1   |
|                                  |      |            |       | Erythroblastosis       | 1   |
|                                  |      |            |       | Prematurity only       | 2   |
| Placenta previa                  | 4    | 6          | 10    | Prematurity only       | 3   |
|                                  |      |            |       | Asphyxia               | 3   |
|                                  |      |            |       | Birth injury           | 1   |
|                                  |      |            |       | Congenital abnormality | 1   |
|                                  |      |            |       | Congenital pneumonia   | 1   |
|                                  |      |            |       | No cause               | 1   |
| Toxemia and/or chronic nephritis | 0    | 6          | 6     | Prematurity only       | 4   |
|                                  |      |            |       | Diarrhea, newborn      | 1   |
|                                  |      |            |       | Maceration             | 1   |
| Cephalopelvic disproportion      | 5    | 0          | 5     | Birth injury           | 2   |
|                                  |      |            |       | Congenital abnormality | 1   |
|                                  |      |            |       | Erythroblastosis       | 1   |
|                                  |      |            |       | No cause               | 1   |
| Cardiac                          | 1    | 1          | 2     | Birth injury           | 1   |
|                                  |      |            |       | Prematurity only       | 1   |
| Constriction ring                | 1    | 0          | 1     | Congenital pneumonia   | 1   |
| Fixed pelvic kidney              | 0    | 2          | 2     | Birth injury           | 1   |
|                                  |      |            |       | Prematurity            | 1   |
| Acute yellow atrophy             | 1    | 0          | 1     | Asphyxia               | 1   |
| Posterior sacculation of uterus  | 0    | 1          | 1     | Prematurity only       | 1   |

Ordinarily we are in the habit of associating birth injuries with the trauma of operative vs. pelvic deliveries or the trauma produced by a forceful rapid labor as the head is driven against a resistant pelvic floor, but apparently it would seem that the forces of labor may cause intracranial injuries under less obvious traumatic conditions. The actual



delivery of the child through the uteroabdominal incision was difficult in only one instance and this might have been the cause of the trauma in that case.

The discussion thus far has brought out the importance of asphyxia, birth injury, and congenital pneumonia as major causes of death in relation to the problems of labor. For this reason it would seem profitable to study these conditions in more detail, especially to determine how these deaths might have been prevented. Table X shows that these major causes of death are more distinctly problems that concern the term infant. The incidence of such deaths among the viable premature infants is decidedly less and in the very small previable premature infants their occurrence is negligible.

TABLE X. RELATIONSHIP OF MAJOR CAUSES OF FETAL AND NEONATAL DEATHS TO THE AGE OF THE FETUS

|                      | PREVAILABLE<br>PREMATURES<br>(92) |     | VIABLE<br>PREMATURES<br>(350) |      | TERM<br>(558) |      |
|----------------------|-----------------------------------|-----|-------------------------------|------|---------------|------|
|                      | NO.                               | %   | NO.                           | %    | NO.           | %    |
| Birth injury         | 0                                 | 0   | 22                            | 6.3  | 91            | 16.3 |
| Asphyxia             | 4                                 | 4.3 | 44                            | 12.6 | 150           | 26.8 |
| Congenital pneumonia | 0                                 | 0   | 7                             | 2.0  | 62            | 9.3  |

The relationship of these major causes of fetal death to the time of death is shown in Fig. 2. The incidence of death due to asphyxia is highest during the ante-partum and intra-partum periods. Asphyxia, therefore, results largely in stillbirths, and it constitutes a distinct problem of labor. It is noteworthy that asphyxia is responsible for only a small number of neonatal deaths. It may well be that serious degrees of asphyxia usually prove fatal before the child is born, while the effects of lesser degrees of asphyxia are overcome once the child is born and respirations have been established. This is not entirely true, however, because there seems to be evidence to suppose that a child who has shown some evidence of intrauterine asphyxia and then is born alive may subsequently develop a pneumonitis from the effects of aspirated material. Such cases naturally would appear in the pneumonia rather than the asphyxia group.

Deaths due to pneumonia occur with greatest frequency during the intra-partum period, but if the child survives labor it is more likely to die at some time after the second hour of birth.

The deaths due to birth injury also occur most frequently during the intra-partum period, but they constitute the largest group that die during the first two hours post partum.

It is interesting to note that the general pattern of the curves noted in asphyxia, pneumonia, and birth injury, changes when the deaths due to prematurity are considered. Here we find that the ratio of stillbirths to neonatal deaths is reversed. Most premature babies die during the first twenty-four hours of life, a point which cannot be overemphasized in reference to their management.

In relationship to the duration of labor, all these major causes of death showed a decided increase in labors of thirty hours or more (Fig. 3).

When the method of delivery is studied in relation to the three major causes of infantile mortality (Table XI), it is noted first of all that the

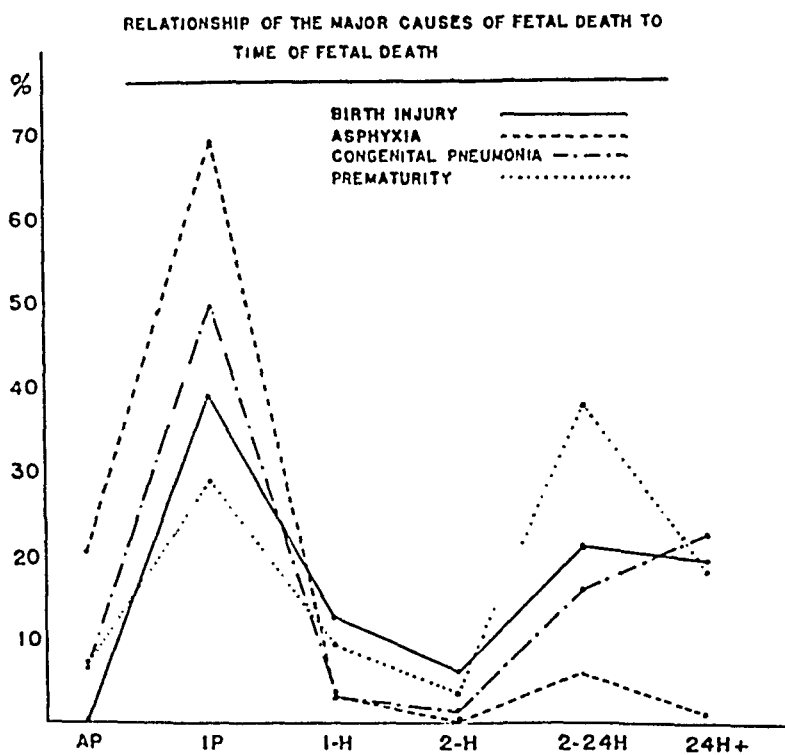


Fig. 2.

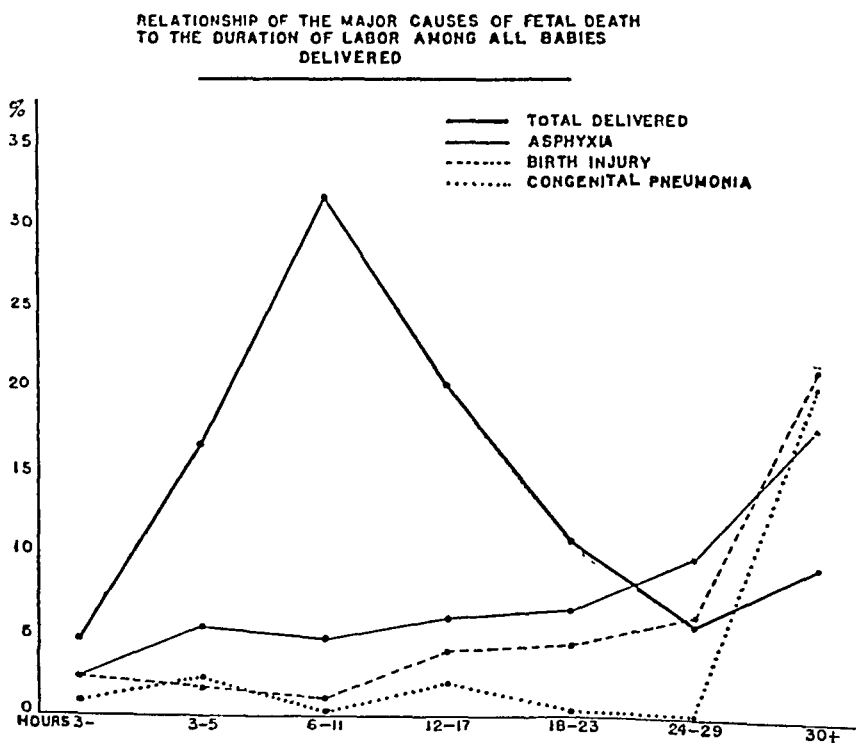


Fig. 3.

TABLE XI. RELATIONSHIP OF THE METHOD OF DELIVERY TO THE MAJOR CAUSES OF FETAL AND NEONATAL MORTALITY

| METHOD OF DELIVERY  | TOTAL DE-LIVERED | DEATHS FROM BIRTH INJURY |      | DEATHS FROM ASPHYXIA |      | DEATHS FROM CONGENITAL PNEUMONIA AND SEPTICEMIA |       |
|---------------------|------------------|--------------------------|------|----------------------|------|---|-------|
|                     |                  | NO.                      | %    | NO.                  | %    | NO.   | %     |
| Spontaneous vertex  | 19,916           | 28                       | 0.01 | 80                   | 0.04 | 28  | 0.01  |
| Low forceps         | 2,672            | 10                       | 0.04 | 26                   | 0.01 | 8   | 0.03  |
| Midforceps          | 1,011            | 29                       | 2.9  | 10                   | 0.01 | 13  | 1.3   |
| Breech delivery     | 1,084            | 18                       | 1.7  | 27                   | 2.5  | 8   | 0.07  |
| Version, extraction | 182              | 12                       | 6.6  | 17                   | 9.3  | 1   | 0.06  |
| Craniotomy          | 38               | 7                        | 18.4 | 3                    | 7.9  | 11  | 28.95 |
| Cesarean section    | 782              | 3                        | 0.04 | 23                   | 2.9  | 1   | 0.01  |
| High forceps        | 29               | 6                        | 20.7 | 3                    | 10.4 | 0   | 0.0   |

birth injuries showed an increasing incidence as the more difficult operations are considered. The lowest incidence appeared in the spontaneous group (0.01 per cent) and the highest in the high forceps group (20.7 per cent). The risk of birth injury is greater in midforceps operations (2.9 per cent) than in breech deliveries (1.7 per cent).

In the cases of asphyxia, a somewhat similar relationship of increasing incidence with operative deliveries is noted. The very low asphyxia incidence in midforceps operations (0.01 per cent) is in contrast to the higher incidence of birth injuries in these operations (2.7 per cent), a point which should be borne in mind when forceps are used to deliver the infant that shows evidence of distress. The high incidence of deaths due to asphyxia among infants delivered by cesarean section (2.9 per cent) is explained by the relatively large number of cases of placenta previa and accidental hemorrhage in which the cesarean section was done primarily for maternal indications.

The deaths in the pneumonia group show no significant relationship to the method of delivery except for the very large number of these infants that were delivered by craniotomy (28.95 per cent). This is simply evidence of the large number of cases of pneumonia that died in utero.

Among all infants delivered at term, the incidence of large babies, which we arbitrarily chose to be 3,600 Gm. or over, was 33.1 per cent (Table XII). By comparison, the incidence of such term infants among

TABLE XII. RELATIONSHIP OF DEAD INFANTS WEIGHING MORE THAN 3,600 GM. TO THE MAJOR CAUSES OF FETAL AND NEONATAL DEATHS

| CAUSES   | NO. OF TERM DEAD INFANTS | NO. WEIGHING MORE THAN 3,600 GM. | RATE (PER CENT) |
|--|--------------------------|----------------------------------|-----------------|
| Birth injury   | 91                       | 46                               | 50.6            |
| Asphyxia   | 147                      | 56                               | 38.1            |
| Congenital pneumonia   | 62                       | 23                               | 37.1            |
| Among all term babies delivered 33.1 per cent weighed 3,600 Gm. or more. |                          |                                  |                 |

the deaths due to birth injury was 50.6 per cent. The large babies among the cases of asphyxia and congenital pneumonia also showed an increase above average but this was less striking than in the cases of birth injuries. Obviously the large size of the baby frequently is over-

looked. The large baby should be given more serious consideration as a problem in dystocia.

In the light of the complete data presented by these cases, it seemed justifiable to study the major causes of infantile mortality from the viewpoint of preventibility. In order to do this, it was necessary first to ascertain the predisposing factors in each death as accurately as the clinical pathologic data afforded. In Table XIII, for example, there are listed in the order of their frequency the predisposing factors in all the cases of asphyxia. We note, first, that 43, or 21.7 per cent, of the patients in this group died from asphyxia which resulted from premature separation of the placenta. From the very nature of this condition, the prospects of materially reducing the resulting fetal loss do not seem too hopeful. As contrasted with placenta previa, in which condition there is also serious interference with the uteroplacental exchange, it can be said that premature separation of the placenta places the fetus in a more precarious situation and the validity of performing a cesarean section in cases of premature separation of the placenta largely on fetal indications, therefore, is open to criticism. In placenta previa there would seem to be more ample justification for including the prognosis to the child in the calculation.

TABLE XIII. PREDISPOSING FACTORS IN ALL CASES OF ASPHYXIA

| FACTORS   | TERM | PREMATURE |
|---|------|-----------|
| Premature separation of placenta                                    | 20   | 23        |
| Tight loop of cord around neck                                      | 26   | 8         |
| Prolapsed cord  | 21   | 3         |
| Placenta previa   | 15   | 8         |
| Prolonged labor with:   |      |           |
| Breech  | 6    | 0         |
| Uterine inertia   | 6    | 0         |
| Inadequate pelvis   | 4    | 0         |
| Failure of cervix to dilate   | 2    | 0         |
| Constriction ring   | 2    | 0         |
| Transverse  | 1    | 0         |
| Not known   | 14   | 0         |
| Death of mother   | 6    | 1         |
| Toxemia   | 4    | 2         |
| Narcosis  | 4    | 0         |
| Breech  | 3    | 0         |
| Terminal premature separation placenta                              | 2    | 1         |
| Ruptured uterus, inadequate pelvis                                  | 2    | 1         |
| Secondary abdominal pregnancy                                       | 2    | 0         |
| True knot of umbilical cord   | 1    | 1         |
| Impacted shoulder, large baby 6,280 Gm. }                           | 2    | 0         |
| 6,240 Gm. }   |      |           |
| Prolapsed arm, inadequate pelvis                                    | 1    | 0         |
| Thrombosis umbilical cord   | 1    | 0         |
| Premature separation of placenta following induction with pituitrin | 1    | 0         |
| Tetany of uterus following induction with pituitrin                 | 1    | 0         |
| Ruptured uterus following induction with pituitrin                  | 1    | 0         |
| Long second stage with inadequate outlet                            | 1    | 0         |
| Severe chill, acute pyelitis  | 1    | 0         |

Among the cases of premature separation of the placenta, there were 3 in which the separation occurred when the head was well down on the pelvic floor. The history of these cases is characteristic. Usually a normal labor without obvious interference to the fetal circulation until

the very end when it is reported that the fetal heart is very slow or has suddenly disappeared. When delivery is effected, the birth of the child is followed by a gush of blood and along with it appears the completely detached placenta. If the attendants are aware that such unfortunate cases of terminal placental separations occasionally occur and keep a constant watch over the fetal heart during the second stage, delivery may be carried out before the asphyxia becomes irreversible. To a large extent, therefore, the small number of deaths due to this type of premature separation of the placenta must be considered preventable.

The asphyxia deaths due to cord complications represent another large group which for the most part cannot be prevented. A study of these cases permits the following conclusions:

1. Cord complications should be suspected always when signs of fetal asphyxia develop in the absence of such maternal conditions as premature separation of the placenta, placenta previa, prolonged labor, and toxemia of pregnancy.
2. With the aim of detecting a prolapsed cord, the general rule is that the fetal heart must be auscultated after the membranes rupture. This would seem to be insufficient in many instances. The fetal heart may be perfectly normal immediately after the cord prolapses only to fail later on. The rule should be to the effect that the fetal heart must be carefully auscultated frequently during the half hour following the rupture of the membranes.
3. When the presenting part is unengaged and the membranes rupture, a cord prolapses often enough to make at least a rectal examination at that time of distinct value.
4. Tight loops of cord around the neck are hardly ever diagnosed until the child is delivered. It seems justifiable to suggest that when no other cause for the asphyxia is apparent, this condition should be suspected and the hand introduced to palpate the neck region. If this condition were known to exist before the actual delivery, the choice of operative procedures employed might be influenced by such knowledge.

The predisposing factors in asphyxia associated with prolonged labors are naturally related to the problems of dystocia in general. While the deaths due to birth injury in the presence of dystocia are not infrequently the result of unwarranted early interference, those due to asphyxia, on the other hand, are not infrequently the result of an overconservative policy of managing the labor. But while this overconservatism was displayed in the actual conduct of the labor, the delivery itself was often hastened because of a slowing fetal heart. If overconservatism in the management of labor proves to be an error, leading to a state of fetal asphyxia, then rapid delivery in the face of a failing heart simply multiplies the error.

While the factors which bring about asphyxia in placental and cord complications are obvious, those which are related to the asphyxia of the prolonged labor are not well understood. It is conceivable that prolonged labor results in intracranial vascular changes which in turn affect the fetal respiratory center, or what seems more likely, the more marked degree of uterine retraction with prolonged labor brings about

a state of relative ischemia of the entire uterine circulation resulting in interference with the efficiency of the uteroplacental exchange and subsequent fetal anoxia. In any event, the treatment of fetal asphyxia should begin by inhibiting uterine contractions with an anesthetic that permits a large admixture of oxygen such as ether. The fetal heart is watched constantly and as long as the rate shows gradual acceleration, even if the degree of such acceleration is slight, no attempt whatsoever is made to deliver the child. Nearly always after a period of five to ten minutes the fetal heart becomes restored to a normal rate. At this stage the mother should be receiving oxygen in maximal amount and just sufficient anesthesia to prevent uterine contractions. Under these conditions delivery may be carried out slowly and deliberately. This method of treating the asphyxiated child falls in line with the present-day surgical principle of treating the patient, which in this case is the unborn child, so that he is in the best possible condition before any surgical procedure is attempted.

Asphyxia was of unknown origin in fourteen term infants. There was nothing about their deaths which we could relate in any way to the mechanism of asphyxia either clinically or pathologically.

Asphyxia was due to toxemia of pregnancy in 6 cases. While the infantile mortality rate is high in severe toxemia, the cause of these deaths is not definitely understood, because the fetus is so frequently macerated that very little pathologic study is possible. While most of the deaths due to toxemia in this series, therefore, are entered in the large group of macerated babies or among the asphyxias due to premature separation of the placenta, a small group showed pathologic evidence of asphyxia without demonstrable cause other than the toxemia. It is assumed that the toxemic state so alters the uteroplacental exchange that the fetal circulation becomes severely compromised.

As we had planned this survey originally, a study of the influence of analgesics on asphyxia and fetal deaths in general was contemplated, but the time intervals of administration of drugs were not recorded with sufficient accuracy to give value to such an analysis. Only isolated instances could be satisfactorily evaluated. There were four cases in which analgesic drugs were given in large enough dosage to be considered unequivocal factors in the asphyxia.

TABLE XIV. PREDISPOSING FACTORS IN ALL CASES OF BIRTH INJURY

| FACTORS   | TERM | PREMATURE |
|---|------|-----------|
| Cephalopelvic disproportion                       | 22   | 0         |
| Uterine inertia (some due to narcosis)            | 16   | 0         |
| Not known   | 11   | 7         |
| Malposition                                       |      |           |
| Breech  | 9    | 5         |
| Brow  | 4    | 0         |
| Face  | 1    | 0         |
| Forceps trauma and/or bad mechanics               | 8    | 1         |
| Rapid, hard labor (some without analgesia)        | 6    | 3         |
| Rapid expulsive labor following medical induction | 3    | 2         |
| Trauma from version, extraction (no other cause)  | 1    | 3         |
| Asphyxia with rapid delivery                      | 3    | 0         |
| Prolonged second stage                            | 3    | 0         |
| Obstruction from myomas                           | 2    | 0         |
| Constriction ring                                 | 2    | 0         |
| Forceps trauma in cesarean section                | 0    | 1         |

In the remainder of the asphyxia group, the cases that merit comment are those in which pituitary extract proved disastrous. Although an indispensable drug, its use before delivery at times becomes hazardous. There were apparently more bad effects when the pituitary extract was administered intranasally. It would seem that when given in this way the dosage is indeterminate and that in some cases more of the drug may be absorbed than can be tolerated with safety. The intramuscular administration starting with doses as low as one minim to ascertain the patient's sensitivity to the drug would seem to be a much safer procedure.

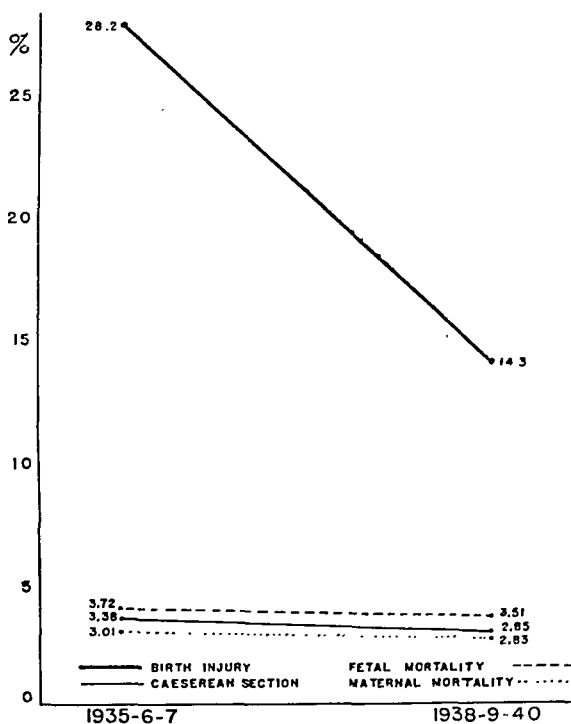


Fig. 4.

As might well be expected, the most important predisposing factor in the cases of birth injury was cephalopelvic disproportion (Table XIV). If the limitations of the pelvis had been accurately known in the 22 cases which fall in this category, a well-timed cesarean section would have saved most of these babies. As these birth injuries were being reviewed, it occurred to us that there were many more such cases among the older records than among the more recent ones. On analysis this proved to be true (Fig. 4). There was a reduction in the incidence of birth injuries from 28 per cent of all fetal deaths in 1935, 1936, and 1937 to 14 per cent of all fetal deaths in the years 1938, 1939, and 1940. This occurred without any rise in the cesarean section or fetal mortality rate. On the contrary, both the cesarean section rate and the fetal mortality rate showed a slight fall in the more recent years. In explaining these results, we believe that adequate emphasis should be placed upon the aid that x-ray pelvimetry has given us. In our combined experiences, this has been the most important contributory factor in the reduction of the incidence of birth injuries. Roentgenologic pelvimetric studies have

not only aided us in choosing the cases of cephalopelvic disproportion early in labor when the cesarean section operation can be done with comparative safety, but they have enabled us to use better mechanics in operative pelvic deliveries.

The cases of birth injury associated with uterine inertia present a real problem, for in this group all the refinements of prognostic acumen may fail. There is no certain method of determining whether a patient with primary uterine inertia will develop efficient uterine contractions as labor advances or continue to have desultory ineffectual pains throughout the entire labor. There is real need for an accurate method by which a qualitative interpretation of the uterine contraction may be made.

In eighteen cases the predisposing cause of the birth injury was not apparent from the records. While this might be expected in a certain number of the premature babies, it is difficult to explain the 11 cases that occurred in term infants. We can only conclude that such factors as cephalopelvic disproportion, forceps trauma, and bad mechanics frequently go unrecognized, although it should be restated here that the forces of labor in the course of molding and descent occasionally may cause damage to the fetal head even when there is no apparent trauma. This was shown in the analysis of the cesarean section group.

Just as there should be condemnation of the excessive use of analgesia leading to a state of uterine inertia, so we condemn the failure to use these valuable drugs when the patient develops unduly forceful frequent contractions that characterize precipitous labors. Rapid labor whether it develops spontaneously or is the result of induction should be treated with proper sedatives or anesthesia to avoid intracranial injury.

A small but sad group of cases are the three babies that sustained intracranial injuries when attempts were made to save them from asphyxia. Again, in these cases, better management of the asphyxiated baby might have given different results.

The factors which predispose to congenital pneumonia (Table XV) seem to fall into a fairly definite pattern. We have first those factors

TABLE XV. PREDISPOSING FACTORS IN ALL CASES OF CONGENITAL PNEUMONIA AND SEPTICEMIA

| FACTORS  | TERM | PREMATURE |
|--|------|-----------|
| Premature rupture of membranes, uterine inertia, prolonged labor, intra-partum infection | 28   | 1         |
| Premature rupture of membranes with normal labor   | 13   | 1         |
| Not known  | 7    | 5         |
| Inadequate pelvis and prolonged labor  | 6    | 0         |
| Prolonged labor and:   |      |           |
| Narcosis   | 2    | 0         |
| Large baby, breech   | 1    | 0         |
| Constriction ring  | 1    | 0         |
| Medical induction  | 1    | 0         |
| Premature rupture membranes and maternal pneumococcus infection                          | 1    | 0         |
| Congenital anomaly of the heart  | 1    | 0         |
| Erythroblastosis   | 1    | 0         |

that predispose to a prolonged labor, namely, uterine inertia and cephalopelvic disproportion, and to them has been added the premature rupture



of the membranes. The problem, therefore, is not fundamentally different from that noted in birth injury and asphyxia, for it could be said that if the membranes had not ruptured many of these babies would have survived up to the time of delivery, only to be subjected to the same hazards encountered in those groups. They belong in the pneumonia group, therefore, rather than in the birth injury or asphyxia group because the accidental early rupture of the membranes exposed them to an infection which caused their death before they could be exposed to trauma or asphyxia.

While this form of reasoning may apply to many of the pneumonia cases, it does not apply to all, for we note that in 14 cases labor was normal and there is every reason to believe that, had the membranes remained intact, a living child would have resulted. There is an important lesson to be learned from these 14 cases in connection with the artificial rupture of the membranes either to induce or hasten labor. While premature rupture of the membranes is not usually attended with serious consequences, the possibility of a fetal pneumonia should not be completely dismissed from the mind. A good rule to follow should be to the effect that the membranes should be preserved at all times unless there is reason to believe that the termination of labor will not be long delayed after their rupture.

In Table XVI it is noted that 27.4 per cent of all premature labors occur without cause. Premature rupture of the membranes could not be listed as a separate predisposing cause of premature labor, because one does not know whether the rupture of the membranes occurs as an accidental predisposing incident unrelated to labor itself or as a concomitant part of the premature labor. It was somewhat surprising

TABLE XVI. PREDISPOSING CAUSES OF PREMATURE LABOR

| CAUSE  | NO. CASES | PERCENTAGE |
|--|-----------|------------|
| No cause (including premature rupture membranes) | 116       | 27.4       |
| Dead fetus                                       | 113       | 26.7       |
| Congenital abnormalities                         | 51        | 12.0       |
| Premature separation of placenta                 | 24        | 5.7        |
| Multiple pregnancy                               | 22        | 5.2        |
| Therapeutic interference                         | 17        | 4.0        |
| Placenta previa                                  | 17        | 4.0        |
| Toxemia  | 13        | 3.1        |
| Hydramnios (no congenital abnormalities)         | 7         | 1.7        |
| Acute pyelitis                                   | 7         | 1.7        |
| Multiple myomas                                  | 6         | 1.4        |
| High amputation of cervix                        | 5         | 1.2        |
| Footling breech                                  | 4         | 0.9        |
| Undelivered                                      | 4         | 0.9        |
| Maternal pneumonia, influenza                    | 4         | 0.9        |
| Cesarean section                                 | 3         | 0.7        |
| Bicornuate uterus                                | 2         | 0.5        |
| Severe anemia                                    | 1         | 0.2        |
| Tuberculosis with high fever                     | 1         | 0.2        |
| Ruptured cesarean scar                           | 1         | 0.2        |
| Following radical mastectomy                     | 1         | 0.2        |
| Following fall                                   | 1         | 0.2        |
| Injection varicose veins with quinine            | 1         | 0.2        |
| Cachexia, gastric cancer                         | 1         | 0.2        |
| Self-induced                                     | 1         | 0.2        |
|  | 423       | 99.6       |

to find so many cases in which there were definite predisposing factors of premature labor. An analysis of these factors brings out a large number of unrelated conditions which throws very little light on the problem of preventability except for (1) 5 patients in whom there had been a high amputation of the cervix, (2) 3 patients in whom a cesarean section was done too early in the period of gestation, and (3) 1 patient who received injections of quinine for the treatment of varicose veins.

#### DISCUSSION

With the realization that the presentation of our study includes many facts which conform to statistics previously reported and substantiates in percentages what some have already known to be true from many years of experience and teaching, we should like to emphasize that our results and observations, entirely based on a critical analysis of all the cases included in the scope of our study, represent the combined experience of the Sloane Hospital for Women and the Lying-in of the New York Hospital. Each history was carefully reviewed, and we feel that the expenditure of time that was demanded fully repaid our efforts, since in most cases we were able to arrive at a satisfactory evaluation of the data recorded.

The results, as they have been reviewed, immediately become associated with the subject of preventability. How might we have arrived at a lower fetal and neonatal mortality rate during the period considered in our analysis? How may we benefit now from our experiences in the immediate past? How will we be able to reduce fetal and neonatal mortality in the future? It would be presumptuous to assume that these questions can be fully and satisfactorily answered. However, in the light of our analysis, the following comments seem worthy of consideration.

A note of conservatism dominates the practice and teaching of obstetrics in the two clinics represented in the study. Although we cherish that note, fair criticism can be directed to a representative number of cases in which earlier interference might have saved the baby. Cases of prolonged labor without appreciable progress leading to fetal distress with subsequent asphyxia and instances in which the presenting part was allowed to remain on the pelvic floor and in midpelvis too long during the second stage are examples.

It appears that a more judicious use of oxygen and ether anesthesia in cases where the fetus begins to show early signs of distress in utero might have prevented fatal asphyxia. Too frequently operative interference by the application of forceps, breech extraction, or version and extraction was untimely hurried in instances of fetal distress, especially when following vaginal examination the cervix was found "almost" completely dilated. More oxygen and ether anesthesia and less hurry might have prevented fetal death under such circumstances.

Asphyxia resulting from terminal separation of the placenta might not have proved fatal with more active vigilance during the second stage.

There were a considerable number of cases in which the cord prolapsed following rupture of the membranes. Since most of these were associated with abnormal presentations and floating heads and because the accident, in many cases, was not detected until a comparatively long interval after its occurrence, it seems that a number of babies might not have died of asphyxia had the obstetrician known of the prolapse promptly and acted accordingly. Patients in active labor with abnormal presentations and floating presenting parts should be carefully followed and examined for a prolapsed cord soon after the membranes rupture.

Too much care and discrimination in the use of oxytocics during labor cannot be exercised. Primary fetal asphyxia and asphyxia secondary to premature separation of the placenta, while only a few in number, resulted from the administration of pituitrin.

A consideration of birth injuries reveals that disproportion and bad mechanics in the application of and extraction with forceps accounts for a greater part of the unhappy outcomes. Unquestionably, a timely cesarean section was indicated and would have saved the baby in many instances. To cope with this problem, it becomes evident that we should be incessantly striving for a more accurate evaluation of each individual case. Today we believe that x-ray pelvimetry is one of the invaluable adjuncts which is enabling us to refine our judgment and decision in making better selection of these cases for cesarean section and forceps delivery.

Medical induction with quinine and with or without pituitrin is not an obstetric procedure without potential hazard. Rapid and expulsive labors following medical induction with subsequent birth injury or asphyxia to the fetus are not rarities. For this reason, only the most justifiable indications should be current whenever a medical induction is contemplated.

The different individual factors and combination of factors influencing fetal mortality are much too great to enumerate and consider. However, prevention of fetal deaths as well as maternal deaths is still intimately related to better ante-partum care, better obstetric training, improvement in operative procedures and techniques, and so far as the neonatal baby is concerned, a better understanding of its immediate pediatric problems.

Primary uterine inertia, premature labor, premature rupture of the membranes, the effect of analgesia on fetal respiration and circulation, the onset and mechanism of labor, are major problems which remain beyond our complete understanding. The hope of the future lies in their solution. True, great strides have been made. For example, researches on x-ray pelvimetry are beginning to give us some insight on the effect

of the forces and mechanism of labor, endocrinology is advancing our knowledge of the physiology of the uterus, and the work of Snyder and many others is contributing newer concepts of intrauterine respiratory physiology and the effect of drugs and anesthetics on fetal respiratory and circulatory centers.

In striving to reduce fetal mortality, we cannot lose sight of its reciprocal, maternal mortality. The two are inseparable so far as they reflect the brand of our obstetric practice, since one cannot be fundamentally sacrificed at the expense of the other. The best obstetrics will always be projected in our constant efforts to reduce both infantile and maternal mortality.

#### SUMMARY

1. The study is concerned with a report of 1,000 fetal deaths occurring among 25,823 deliveries at New York Hospital and the Sloane Hospital for Women. On the basis of live births, the gross fetal mortality rate was 4.03 per cent. If only the viable infants are included, the rate is 3.66 per cent.

2. Asphyxia is the most common cause of fetal death.

3. There is a higher fetal death rate in the Negro.

4. Multiparas and primiparas show essentially the same fetal death rate.

5. The greatest net gain of living over dead children occurs among women between 20 and 24 years of age. After the age of 30 the woman delivers a proportionately greater number of dead babies than she did before that age.

6. In labors that exceed thirty hours, the fetal mortality rate doubles.

7. Spontaneous deliveries show the lowest fetal death rate. High forceps show the highest.

8. On the basis of the material studied, a reduction of the fetal death rate suggests the following:

- (a) Labors that exceed thirty hours in duration should receive the benefit of consultation, unless delivery is imminent.

- (b) Interference should be avoided unless absolutely justifiable; the best results are obtained in spontaneous deliveries.

- (c) Pelvic conformation should be studied roentgenologically if there is doubt. Both see and feel the cephalopelvic relationship.

- (d) The mechanism of delivery should be adapted to the architecture of the pelvis in operative deliveries.

- (e) In dystocia, avoid interference if progress is being made even though the progress is slow, but do not unnecessarily delay delivery if progress has come to a standstill.

- (f) The asphyxiated baby should be treated before delivery. Avoid hurry in delivering these babies.

- (g) The fetal heart should be auscultated frequently for one-half hour after membranes rupture.

(h) Examine patient after the membranes rupture if the presenting part was high prior to their rupture.

(i) Examine for tight cord around neck when there is no other obvious cause for asphyxia.

(j) Use sedatives sparingly when labor is going to be prolonged. Use them freely in cases of precipitate labors.

(k) Use pituitrin with great care if at all before parturition.

(l) Save premature babies by adequate pediatric organization. The first twenty-four hours are the most important.

(m) Research in the causes of labor, the causes and early detection of uterine inertia, the causes of premature rupture of membranes, means of predetermining the size of the fetus, the physiology of fetal respiration, the mechanics of molding and birth injuries, and the physiology of the premature infant will all aid materially in further reducing the infantile mortality rate.

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## THE CLINICAL SIMILARITY OF CORPUS LUTEUM CYST AND ECTOPIC PREGNANCY

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THERE is, perhaps, no better known and no more dramatic condition in gynecology than that of ruptured tubal pregnancy with massive intraperitoneal hemorrhage. The classical picture of sudden, severe, tearing pain in the lower abdomen followed by shock in a woman of childbearing age offers little chance for diagnostic error. It is, moreover, not essential that the diagnosis in such instances be precise, for laparotomy is obviously and urgently required. A diagnostic problem is encountered, however, in either the unruptured variety of tubal pregnancy or the type which causes a slow intra-abdominal hemorrhage through the tubal lumen, tubal abortion. Many of the patients coming within either of these two groups of tubal gestation, the unruptured and the tubal abortion, present symptoms so mild, complaints so bizarre, and physical signs so vague that it is not unusual for the illness to be misinterpreted. When the patient's history fits into the textbook pattern of ectopic gestation, irregular uterine bleeding following a missed period and accompanied by recurrent episodes of lancinating pain in the lower abdomen, its recognition offers little difficulty. This conventional clinical picture of either unruptured tubal pregnancy or tubal abortion is, however, occasionally mimicked to a most surprising degree by another, less serious, intrapelvic disorder, the corpus luteum cyst.

Rokitansky described the corpus luteum cyst as a pathologic entity in 1859. Years later, when ovarian changes were first being correlated with aberrations of the menstrual cycle, several gynecologists (R. Meyer, Ruge II, Pischzek, and others) observed the association of delayed menstruation with the persisting, usually cystic, corpus luteum. The clinical similarity of tubal abortion and corpus luteum cyst was first recognized by Halban<sup>1</sup> in 1915. In reporting his several experiences in mistaking a simple lutein cyst for tubal gestation, Halban stated: "The usual story is that a woman reports with the complaint of early amenorrhea, believing herself pregnant. The examination reveals a slightly enlarged uterus and, more important, a soft tumor in either the right or the left adnexa. If the physician knows the patient and recalls that no such tumor was present at previous examinations, he must entertain the suspicion that he is dealing with an extrauterine pregnancy. Such a suspicion led me in several instances to perform a laparotomy with the expectation of removing a pregnant tube. In place of this, however, a cystic tumor of the ovary and no trace of ectopic pregnancy was found."

Every gynecologist sooner or later experiences similar chagrin and surprise after performing a laparotomy on a patient with a seemingly typical example of tubal abortion only to be quite taken aback in discovering a small and relatively insignificant corpus luteum cyst. While this simulation is widely recognized, it is not generally appreciated that the laboratory findings in these two conditions may be alike.

This presentation was undertaken not only to re-emphasize the remarkable resemblance which the syndrome created by an abnormally persistent corpus luteum may bear to extrauterine pregnancy, but also to draw attention to the fact that the degree of mimicry may be heightened, as illustrated in the histories abstracted herein, by the presence of a positive Friedman test and the finding of well-developed deciduilike changes in the endometrium.

#### PATHOGENESIS OF THE CORPUS LUTEUM CYST

The etiology of the simple retention cyst of the corpus luteum is not clear. "It is possible," states Novak,<sup>2</sup> "that at times the cystic distention of a corpus luteum for some unknown reason is so great as to interfere with the normal involution of the lutein layer, thus resulting in the so-called *corpus luteum persistens*." Inasmuch as the corpus luteum cyst is usually found in an otherwise perfectly normal ovary of a woman free from any recognizable ailment, the mechanism of its formation is usually rather loosely ascribed to "perverted physiologic activity."

Shortly after Halban's description of the clinical syndrome, Wagner,<sup>3</sup> in reporting two instances of a falsely positive Aschheim-Zondek pregnancy test in association with a corpus luteum cyst, postulated the origin of the cyst to be hyperpituitary function. One of Wagner's patients exhibited the signs and the symptoms of a benign pituitary adenoma which seemingly yielded to roentgen ray treatment. Others, who obtained a positive biologic pregnancy test in the presence of surgically proved instances of corpus luteum cyst, also assumed that the

presence of an excessive quantity of hypophyseal gonadotropin is responsible for both the persistent corpus luteum and the positive pregnancy test.<sup>4</sup>

Although it is a most attractive and simple theory, it cannot yet be unequivocally stated that the corpus luteum cyst is the result of disordered pituitary function. It can be stated, on the basis of the clinical data and the pathologic findings, that such a cyst represents an abnormal retrogression of the lutein stage and that its association with an excessive excretion of gonadotropin suggests the existence of a temporary state of hyperpituitarism.

Pathologically, a corpus luteum cyst must be differentiated from the follicle cyst and the atretic follicle cyst, and from the mature corpus luteum. All of these structures may be similar macroscopically, attaining the maximum size of a walnut and possessing a small central cavity filled with either coagulable serum or blood. The yellow color often exhibited by the smooth, glistening interior of such a walnut-sized cyst is not necessarily pathognomonic of corpus luteum tissue. The yellow hue may, of course, represent lutein cells, but it may also be derived from lipoid deposits, blood pigment within phagocytes, or luteinized cells of the theca interna.<sup>5</sup> Microscopic study of the wall of such yellow cysts enables one to distinguish the basic morphology. The follicle cyst is identified by the characteristic granulosa cells and the small, crowded cells of the surrounding theca interna. The atretic follicle cyst is recognized by the flattened granulosa layer and the well-preserved, often luteinized, cells of the theca interna. The mature corpus luteum is characterized by its layer of large, polyhedral lutein cells, the outer border of which is penetrated at intervals by v-shaped, capillary-laden bands of luteinized theca cells.

The corpus luteum cyst, representing merely the persistent shadow of a formerly mature corpus luteum, exhibits the substance of the latter in altered form. The histologic appearance of the cyst depends on its age. In the beginning, the lutein layer may be fairly well preserved (Fig. 2). As the blood supply diminishes, fatty degeneration and fibrosis so change the architecture of the layer that it is often unrecognizable. Moreover, its formerly large cells become pyknotic as a result of compression by the semisolid coagulum of the cystic cavity. As time goes on, connective tissue is deposited between the lutein tissue and the centrally contained material, a process which finally results in a densely fibrinous inner lining (Fig. 1).

#### DIFFERENTIAL DIAGNOSIS OF CORPUS LUTEUM CYST AND TUBAL ABORTION

It would be well were one able to differentiate an ectopic gestation from a corpus luteum cyst preoperatively, because the latter does not usually require surgical intervention. The clinical attempt to distin-

guish the two conditions must take into consideration the likeness in symptomatology, the similarity of the pelvic signs, and a possible parallelism of certain laboratory findings. The latter may include an excessive excretion of gonadotropin, the histologic characteristics of the endometrium, and the urinary level of pregnanediol. The brief discussion and the several case histories presented in the following paragraphs do not clarify the problem of establishing a correct preoperative diagnosis. They serve rather to reassert the frequent impossibility of so doing and to surround such errors in diagnosis with an aura of plausibility.

*Symptomatology.*—The symptoms evoked by the persisting corpus luteum and its eventual successor, the corpus luteum cyst, vary with the passing of time. The clinical pattern parallels the gradual change from an active gland of internal secretion producing estrogen and progestin to a functionless, vestigial-like cyst. There is at first a brief period of amenorrhea which is followed, as the luteal tissue distinegrates, by an episode of irregular uterine bleeding. It is this reversal of menstrual function, together with the tender adnexal mass it creates, which causes the corpus luteum cyst to be confused with extrauterine pregnancy. The clinical parallelism may be magnified by the presence of certain of the presumptive signs of pregnancy in women with a persistent corpus luteum. Van Tongeren<sup>6</sup> and others, commenting on the semblance of this condition to pseudopregnancy in animals, reported concerning the presence of vaginal lividity and cervical softening in such patients. The occurrence of these changes, evidence of a superabundance of the ovarian hormones, is readily understood when it is recalled that functioning lutein cells secrete *both* estrogen and progestin. The following case history illustrates the deceptive symptoms and the misleading local signs of pregnancy sometimes evoked by the corpus luteum cyst:

CASE 1.—(Mount Sinai Hospital, No. 95874.) M. V., a secundipara, aged twenty-five years, regular menstrual cycle every thirty days, had had her last menstrual period on July 20, 1935. The August and September periods had been missed, and the patient thereafter experienced brief, recurrent episodes of lancinating pain in the left lower portion of the abdomen. On September 27, believing herself pregnant, the patient attempted to induce an abortion by introducing a rubber catheter into the cervical canal. Several days later, slight bleeding ensued and persisted intermittently for a month, in association with repeated attacks of the left-sided pain and without the passage of either clots or tissue. On November 6, a Friedman pregnancy test was negative. At the time of her hospitalization on November 8, examination showed cyanosis of the vagina, softening of the closed cervix, suspected uterine enlargement, and a plum-sized mass of the left adnexa. The latter seemed unusually tender. The following day, a small quantity of grossly nondescript endometrial tissue was recovered from the uterine cavity by curettage, and exploration of the abdomen revealed a thick-walled, corpus luteum cyst of the left ovary which was removed. Histologically, the endometrium was hyperplastic but showed several areas of secretory change, and the corpus luteum cyst possessed a densely fibrinous lining, a finding which affirmed the apparent chronicity of the cyst (Fig. 1).



*Pelvic Examination.*—The local characteristics of the corpus luteum cyst are not sufficiently distinguished by bimanual pelvic examination to enable a clear differentiation from early tubal pregnancy. The cyst is usually palpable as a walnut-sized, smooth, somewhat mobile, adnexal tumor. Its consistency varies with the content of its central cavity, being either soft or tense. Unless it is ruptured, an event occasionally caused by the bimanual examination, and associated with intraperitoneal bleeding, the corpus luteum cyst is ordinarily much less tender to palpation than the average tubal gestation. This alone, however, is not a sufficient criterion upon which to base a differential diagnosis. The following case report emphasizes the possible error which might occur when there is a too eager interpretation of a tender adnexal mass as a tubal pregnancy:

CASE 2.—(Mount Sinai Hospital, No. 10896.) N. L., a tertipara, aged 23 years, was admitted to the hospital on July 20, 1937, because of repeated attacks of sharp pain in the right lower abdomen during the



Fig. 1.—Photomicrograph of corpus luteum cyst (Case 1), showing a dense layer of fibrin between the central cavity and the lutein cells.  $\times 135$ .

preceding five days. Her menstrual cycle was of the twenty-five-day type, and the last period on June 30 had been scanty. Vaginal spotting was noted on July 18, three days after the onset of abdominal pain. Examination showed a soft, tender, right adnexal tumor the size and shape of a hen's egg. Abdominal exploration, on the provisional diagnosis of unruptured tubal pregnancy, revealed the palpable mass to be a corpus luteum cyst containing a soft blood clot. On histologic study, the lutein cells were clearly recognizable (Fig. 2).

*Excretion of Gonadotropin.*—The biologic pregnancy test, depending upon the excretion of chorionic gonadotropin in the urine of the pregnant woman, is of no value in differentiating intrauterine from ectopic pregnancy. It is generally conceded, however, that the test when positive is important in distinguishing tubal pregnancy from all other recent adnexal masses. Since a positive Aschheim-Zondek or Friedman test in pregnancy indicates living chorionic tissue, a negative reaction

merely implies the converse, the absence of living chorionic tissue. It is possible, therefore, to obtain a negative biologic test in instances of tubal gestation wherein the conceptus has ceased to grow. Experience has proved that a negative Friedman test does not exclude the possibility of ectopic pregnancy and is, thus, meaningless in the differential diagnosis of a tender adnexal tumor. When such a mass is under alert scrutiny, the value of a thoroughly trustworthy positive pregnancy test becomes apparent. The observations of other gynecologists<sup>3, 4</sup> concerning the falsely positive pregnancy test associated with the persistent corpus luteum cast a shadow of doubt upon the reliability of the positive reaction under circumstances leading to the suspicion of ectopic pregnancy. The two case histories which follow serve as practical illustrations of this problem:

CASE 3.—(Hospital of the University of Pennsylvania, Gyn. Nos. 24761 and 24784.) H. F. W., a secundipara, aged 24 years, who



Fig. 2.—Photomicrograph of corpus luteum cyst (Case 2) in which the theca interna, layer of lutein cells and the loose central coagulum are clearly recognizable.  $\times 95$ .

normally had menstrual cycles with a twenty-eight-day interval and a seven-day flow, had had her last menstrual period on Jan. 8, 1935. On February 13, when her expected period was a week overdue, vaginal spotting and intermittent, colicky pain in the lower abdomen occurred. A Friedman test for pregnancy was positive at that time. On February 25, she was admitted to the hospital because of persistence of both the slight metrorrhagia and the pain. Pelvic examination disclosed no abnormalities other than a retroflexed uterus which was easily placed into an anterior position and maintained therein by a Hodge vaginal pessary. The patient was discharged in twenty-four hours, the diagnosis being "early threatened abortion complicated by uterine malposition." She was readmitted ten days later, on March 8, because of increased uterine bleeding and localization of the recurrent pain in the right lower portion of the abdomen. Bimanual examination under anesthesia, following the removal of the pessary, revealed a tense, walnut-sized mass to the right of a retroflexed uterus of normal size. Diagnostic curettage

disclosed no signs of trophoblastic tissue (Fig. 3). Laparotomy showed the adnexal tumor to be a hemorrhagic corpus luteum cyst (Fig. 4).

CASE 4.—(Hospital of the University of Pennsylvania, Gyn. No. 25377.) A. M., a tertipara, aged twenty-eight years, whose menstrual cycle usually had thirty days of interval and three days of flow, was admitted to the hospital on Sept. 19, 1935, because of suspected ectopic gestation. Her last period, on July 6, had been but a "15-minute flow."



Fig. 3.—Photomicrograph of specimen of endometrium (Case 3) recovered by curettage, showing no chorionic villi. Note the decidua-like stromal cells.  $\times 250$ .



Fig. 4.—Photomicrograph of hemorrhagic corpus luteum cyst (Case 3). Note the blood clot adherent to the layer of lutein cells.  $\times 135$ .

Morning nausea and vomiting, mastalgia, and stabbing pain of the lower abdomen occurred early in September. Friedman test was positive on September 15. Examination revealed a normal uterus and exquisitely tender right adnexa. No mass was delineated. Diagnostic curettage recovered a scanty quantity of endometrial tissue. Abdominal exploration disclosed, in addition to tuberculosis of the ileum, a follicle cyst of the right ovary containing a fresh blood clot and showing on histologic study, luteinization of the granulosa cells (Fig. 5).

The two histories abstracted above emphasize the well-known fact that a positive Friedman reaction also occurs in a wide variety of conditions other than pregnancy, conditions which are associated with an *excessive* excretion of gonadotropin. In the absence of chorionic tissue, the Friedman test may, therefore, be considered a fairly good qualitative measure of overactivity of the anterior lobe of the pituitary gland. When faced with the necessity of interpreting such a positive Friedman test, the physician must consider several clinical possibilities. This dilemma is well stated by McCullagh and Cuyler,<sup>7</sup> as follows: "Theoretically, an excess of pituitary gonadotropic hormone might be expected in cases of tumor, and irritative lesions of the pituitary. It should occur in cases of pituitary hyperactivity caused by excessive stimulation from the nervous controlling mechanism, or in the presence of hyperactivity resulting from deficiency of the normal inhibiting factors such as might result from damage to the ovaries or testes." Accordingly, the positive

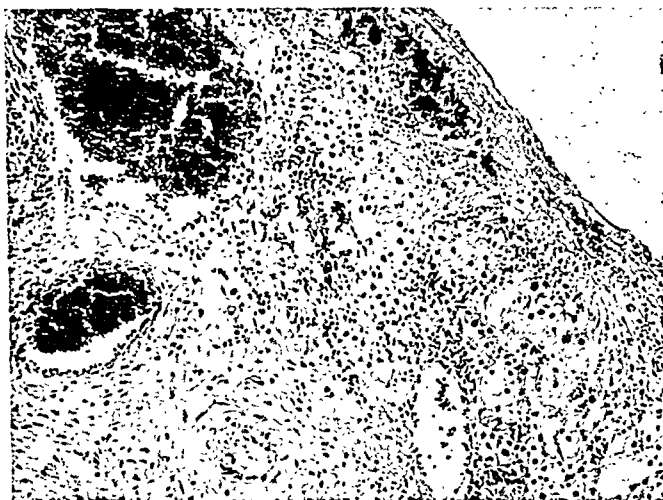


Fig. 5.—Photomicrograph of corpus luteum cyst (Case 4), showing intense hyperemia and well-preserved lutein cells.  $\times 135$ .

Friedman reaction in nonpregnant women with a corpus luteum cyst may be the result either of an unknown disorder affecting the little understood nervous center of the anterior hypophysis or of a diminished production of progesterin and estrogen by the lutein cells. Nothing can be said at the present time concerning the former possibility. However, the latter, subnormal endocrine function of the granulosa cells at the very onset of luteinization, affords a logical, theoretical explanation for the presence of excessive pituitary gonadotropin in the urine. The anterior hypophysis, uninhibited by the low level of ovarian hormones, secretes additional gonadotropic substance in order to support the apparent failure of luteinization and responds too generously. The inordinate quantity of pituitary gonadotropin so produced may result in both the positive Friedman reaction and the oversupported, nonregressive, persistent corpus luteum. This credible hypothesis, as previously noted, is not readily proved.

*Endometrial Pattern.*—The development of decidual changes in the endometrium in association with ectopic pregnancy is universally con-

ceded. However, the number of patients in whom it is found is equivocal, varying inversely with the prior duration of the uterine bleeding.<sup>8</sup> The probability of recovering decidua from the curettings naturally lessens as the time of the bleeding lengthens because the decidual tissue is shed constantly as small fragments. Uterine curettage is, therefore, of some diagnostic value in obscure instances of suspected ectopic pregnancy only if the period of uterine hemorrhage is short. While the presence of decidua without chorionic villi may be considered presumptive evidence of extrauterine pregnancy, its absence under such circumstances does not necessarily exclude the possibility. The interpretation of the curettings obtained for diagnostic purposes in a patient presenting the history of an extrauterine pregnancy is made more difficult by the fact that excessive and prolonged action of the corpus luteum may create a deciduallike pattern in the endometrium (Figs. 3 and 6). The degree of pseudodecidual response in the endometrium depends, quite naturally, on the quantity of progesterin secreted by the corpus luteum. Since this function of the lutein cells apparently varies widely, as gauged by the fluctuations in the amount of progesterin excreted in the urine as pregnanediol during the luteal phase of the menstrual cycle in normal women,<sup>9</sup> it is readily understood that all gradations of pseudodecidua may be encountered. Te Linde and Henriksen<sup>10</sup> recently drew attention "to the possibility of a deciduallike response of the endometrium to progesterone in the absence of pregnancy." The latter authors described several patients with decidual reaction of the endometrium in whom the presence of pregnancy seemed to be either well excluded or quite improbable. The photomicrographic evidence presented and the literature cited by Te Linde and Henriksen substantiate the belief that it is possible for decidua to form in the absence of a fertilized ovum. The endometrium of one of the patients in this series, whose case history follows, presented an excellent example of such pseudodecidua:

CASE 5.—(Mount Sinai Hospital, No. A 14204.) J. R., a secundipara, aged thirty-six years, who usually had a twenty-eight-day menstrual cycle, was admitted to the hospital on Aug. 1, 1939, because of the suspicion of tubal abortion. Her last period had been skipped. Vaginal spotting occurred initially early in July. Cramplike pains, localized to the lower right abdomen, first appeared on July 20. During the succeeding ten days, both the staining and the pain persisted intermittently. The only finding disclosed by examination was a smooth, tense, oval mass to the right of a softened, normally-proportioned uterus. The mass was the size of a walnut and moderately tender. A diagnostic curettage revealed the uterine depth to be 8.0 cm., and recovered a moderate quantity of smooth endometrium. An immediate laparotomy uncovered the presence of a lutein cyst of the right ovary which was resected. The histologic study of the endometrium showed a well-developed progestational tissue with several areas suggesting decidual change but no chorionic villi (Fig. 6). The excised luteal tissue was relatively well preserved.

The dubious significance of decidual changes without chorionic villi in the endometrium, when found in a patient suspected of having either an extrauterine gestation or merely a persistent corpus luteum, is further lessened by the possibility of an earlier complete abortion of an

intrauterine pregnancy. In such an instance, termed "occult pregnancy" by Robert Meyer,<sup>11</sup> the conceptus is allegedly expelled completely, leaving no trace of chorionic villi. While it is possible that such an abortion might occur without leaving macroscopically recognizable remnants of fetal tissue, it is hardly conceivable that a few chorionic villi would not be visible microscopically. This is of some importance clinically, because, in performing a diagnostic curettage to exclude the presence of an intrauterine pregnancy in a patient suspected of having a tubal abortion, the gynecologist rarely employs the frozen section method of immediate microscopy. If the curettings are scanty and appear, on macroscopic inspection, to be free from chorionic elements, laparotomy usually follows. That the chance of error, under such circumstances, is not merely an academic problem but a very practical one, is illustrated by the following case history:

CASE 6.—S. C. (Mount Sinai Hospital, No. 106696), a tertipara, aged 24 years, who normally had a menstrual cycle of twenty-eight-day



Fig. 6.—Photomicrograph of specimen of endometrium (Case 5), showing the pseudo-decidual character of the glands.  $\times 250$ .

intervals and a four-day flow, was admitted to the hospital on April 10, 1937. She stated that her last period had begun on February 24 and had been unusually scanty, lasting only a few hours, and that the period expected on March 24 had been missed. Irregular uterine bleeding, accompanied by brief spells of vertigo and by intermittent, sharp pain in the left lower abdomen, had begun on April 5. On April 10, examination showed a smooth, tender, doughy, thumb-sized tumor of the left adnexa. There were no signs suggestive of an abortion. Diagnostic curettage revealed a uterine depth of 8.0 cm., and a small quantity of endometrium which was grossly interpreted as being "normal." An immediate laparotomy revealed only a tense, blood-filled corpus luteum in the left ovary which was resected. On histologic study, the curettings showed decidua and chorionic villi, and the excised ovarian tissue a well-vascularized corpus luteum.

In a recent communication describing the endometrium of a patient proved to have a persistent corpus luteum, Black and his associates<sup>12</sup>

reported the presence of stainable fat globules in the basal portion of the uterine gland cells as being a characteristic feature of a well-developed secretory endometrium. This confirmed the earlier observations of Aschheim<sup>13</sup> who was the first to draw attention to the basal or infranuclear location of the intracellular lipid substance in the endometrial glands during the premenstrual phase of the cycle. Although the finding of such infranuclear fat droplets may in the future be accepted as an indicator of the response of the endometrium to an adequate supply of progestin, it cannot be looked upon as a criterion of differentiation between a persistent corpus luteum cyst and ectopic gestation. Gillman<sup>14</sup> showed that the basal fat in the gland cells also increased during early pregnancy, suggesting that its appearance is in some manner related to the metabolism of progestin.

*Excretion of Pregnanediol.*—The finding of pregnanediol, the catabolic derivative of progestin, in the urine is considered to be an evidence of the current metabolism of progestin and is interpreted as a signpost of the existence of functioning lutein cells in the ovary.<sup>9</sup> It is to be expected, therefore, that a persistent corpus luteum will be accompanied by an excretion of pregnanediol just as long as the lutein cells function. No information is, however, available concerning the excretion levels of pregnanediol in women proved to have such a functioning corpus luteum cyst. There is, moreover, reason to believe that even if the quantity of pregnanediol excreted by such women were known it would be of little diagnostic value in the presence of signs and symptoms suggesting a tubal gestation. The latter condition, depending for its continued growth on the coexisting corpus luteum of pregnancy, is also accompanied by the excretion of pregnanediol in the urine.<sup>15</sup>

#### MANAGEMENT OF THE PROBLEM

The persistent corpus luteum, simulating ectopic pregnancy, is not encountered often enough to warrant its consideration as a serious problem in differential diagnosis. Even if the preoperative error in diagnosis were more common than it is, the fact that there is no expectant treatment of ectopic pregnancy would not permit surgery to be withheld in many of the instances under discussion. Once the diagnosis of tubal pregnancy is made, the more immediate the surgery the better. When, however, there is some doubt concerning the interpretation of an adnexal mass in association with a history suggesting the presence of either unruptured tubal pregnancy or tubal abortion, conservatism in the form of vigilant observation in a hospital is justified. The period of time to be devoted to such alert watchfulness cannot be dictated by generalities but must be decided for each patient individually.

The histories of the five patients recorded in the foregoing paragraphs pertinently emphasize the probable value of a period of careful observation in the hospital for patients suspected of harboring either a tubal abortion or a corpus luteum cyst. This should be permitted under the watchful eyes of a house staff informed of the diagnostic possibilities.

When, in such a patient, there is an increase in either the objective signs or the subjective symptoms, operation is obligatory. If, on the other hand, the severity of the syndrome under suspicion abates, operation may be held in abeyance until there are definite assurances of the patient's recovery. In occasional instances, needless laparotomy may be avoided by the physician's good judgment and brave patience, two virtues which are fathered only by experience.

#### SUMMARY

1. The history, pathogenesis, and histology of the corpus luteum cyst are briefly reviewed. It is emphasized that, aside from being recognized as a perversion of physiology often attributable to temporary hyperpituitarism, little is known concerning its etiology.

2. The clinical similarity of the corpus luteum cyst and certain types of ectopic pregnancy, an observation credited to Halban, is discussed. It is shown that both conditions may present identical symptoms and pelvic signs, as well as similar laboratory findings.

3. Five patients, each of whom had a corpus luteum cyst preoperatively diagnosed ectopic pregnancy, are cited. The condensed histories and the accompanying illustrations sufficiently exemplify the ample reasons for the diagnostic errors, including the presence of a falsely positive biologic pregnancy test in two instances.

4. The probable physiologic mechanisms of the excessive excretion of gonadotropin (positive Friedman test) and of the deciduallike pattern of the endometrium, both of which are shown to be possible in association with a corpus luteum cyst, are described.

5. It is suggested that even if patients with a suspected adnexal tumor and a history *suggestive* of ectopic gestation were not operated upon immediately but were first carefully observed in a hospital for several days it would be difficult to escape the possibility of an occasional needless abdominal operation.

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2116 SPRUCE STREET

## RENAL AND URETERAL CALCULI IN PREGNANCY\*

WITH AN ANALYSIS OF TWENTY CASES\*

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**C**ALCULOUS disease of the urinary tract is an infrequent but significant complication of pregnancy. Although an enormous literature has accumulated on the subject of urolithiasis, it is interesting that, so far as we can ascertain, exclusive investigations of the association of stones with pregnancy have been scant. Crabtree and Prather<sup>1</sup> have included a consideration of this problem in a broad study of urinary tract infection in pregnancy. Interesting isolated cases have occasionally been reported such as that noted by Young and Carver<sup>2</sup> who observed a case of bilateral cystine renal calculi in pregnancy. Incidental mention also is noted, such as Turley's discussion of Allen's<sup>3</sup> paper on fibrin calculi. We have felt, therefore, that an individualized study is indicated of the numerous significant implications regarding the etiology, diagnosis, treatment, and potential complications of this condition.

### ETIOLOGY OF CALCULI IN PREGNANCY

*A. General Considerations.*—The recent studies of Randall<sup>4</sup> have contributed much to our concept of stone formation. Formerly, the etiology of urinary calculi was classified into two groups. The *primary* calculus was the type for the origin of which there could be found no reasonable explanation. Such a patient generally presented himself or herself with a typical clinical picture of renal colic and then later passed a stone. Subsequent inquiry into the history, physical examination, laboratory and roentgenographic reports failed to reveal the pathologic processes underlying this stone formation. This is the type of calculus which Randall and his co-workers showed to be the result of the deposition of calcium salts in nature's attempt to repair damaged tissue in the renal papilla; this plaque acted as a nidus which induced a disturbance in the colloidal balance of the salts in the calyceine urine with

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their subsequent crystallization. The *secondary* variety of renal calculi have included those stones for which the etiology could be explained on the basis of some altered physiologic or pathologic causal factors, i.e., nutritional deficiency (vitamin A), hyperparathyroidism, infection superimposed on stasis, etc.

*B. Alterations in Mineral Metabolism During Pregnancy.*—It should be realized from the outset that blood calcium readings are not reliable criteria of the calcium content of the tissues. For example, a calcium deficiency may be present despite normal blood calcium readings. The reason for this is that the calcium reserves in the muscle, bones, and other tissues must be appreciably depleted before a hypocalcemia results. Similarly, Toepfer and Sherman<sup>5</sup> have demonstrated the fact that growth and body calcium economy can be stimulated to higher ranges of activity by liberal increases in the calcium or calcium and phosphorus factors in the diet. The potential importance of this somewhat voluntary control of mineral metabolism becomes readily apparent when it is realized that aberrant metabolic changes in body calcium may occur even during normal pregnancy. Apperman<sup>6</sup> has pointed out that flat calcareous plaques are noted frequently on the maternal surface of the placenta; Frankel showed that these were infiltrations of calcium into the necrotic tissue in the region of the terminal portions of the fastening villi, as well as in the external layer of the decidua serotina. He also refers to Rokitansky's description of "puerperal osteophytes"; these are "irregularly shaped plaques of porous, newly formed bone or osteoid tissue found on the internal surface of the cranial bones."

*C. Urinary Stasis and Infection During Pregnancy.*—Within recent years, it has been clearly shown that more than 85 per cent of pregnant women have demonstrable changes in the ureteral tone and anatomic character of the upper urinary tract. Beginning at the termination of the first trimester, the fundamental contributing factors to this metamorphosis are the pressure exerted by the gravid uterus and the hormonal reorganization associated with pregnancy. The effect is essentially a diminution in the peristaltic tone of the ureter and a dilatation of the calyceal system, pelvis, and ureter. A physiologic hydronephrosis and hydroureter may therefore occur. These changes are both more frequent and more marked on the right side, probably due to the extrinsic force presented by the uterus after it arises out of the true pelvis. The tendency to recession to the normal anatomic and physiologic status commences during the last trimester and is generally achieved at six to eight weeks post partum; the latter depends upon several factors, especially the presence of pyelitis during pregnancy as pointed out by McConnell and Gray.<sup>7</sup> The significance of these alterations in the aqueduct system of the upper urinary tract is that the associated urinary stasis provides a fertile culture media for any potential infection.

The incidence of renal infection in pregnancy and the puerperium has been reported to be fairly uniform (2.58 per cent, Herman and Muckle;<sup>8</sup> 2.4 per cent, Abeshouse, Linas, and Kolman<sup>9</sup>).

Urinary stasis, per se, has been shown not to be the primary responsible requisite for the formation of urinary calculi. Infection, however, superimposed on long standing stasis may be influential in calculous formation.

*D. Endocrine Factors.*—Any direct causal relationship between urolithiasis and endocrine factors which are at operation during pregnancy still remains to be worked out. In this connection, it is interesting to note the findings of Burns and Schenken<sup>10</sup> who treated male mice with estrogens. They report an appreciably higher incidence of urinary calculi appearing at an earlier age in the treated (33.1 per cent) than in the untreated (4.1 per cent) animals.

When the changes in the mineral metabolism are considered in relation to stasis and infection, it is remarkable that a greater incidence of urolithiasis is not observed in pregnancy.

#### ANALYSIS OF CASES

The present communication is a critical analysis of 20 patients who were found to have renal or ureteral calculi during pregnancy. The group includes 8 patients admitted to the Chicago Lying-in Hospital during the thirty-month period ending July, 1935, the data of which were presented by one of us (R. A.) before a sectional meeting of the American College of Surgeons, together with 12 cases observed at the Louisiana Charity Hospital in New Orleans in the eighteen-month period ending Oct. 1, 1941. This series does not include any instance in which the stone was not definitely diagnosed or any cases in which gestation was not proved. Bladder stones were also excluded.

*Incidence.*—During the period of eighteen months from which this study was made, 82,034 patients (35,701 males and 46,333 females) were admitted to the Charity Hospital of Louisiana at New Orleans. Of this number, 156 patients were discharged with the final diagnosis of either renal or ureteral calculi, a general incidence of 1:525. These were divided according to sex distribution into 111 males and 45 females (ratio 2.5 to 1). This compares favorably with the findings of Bumpus and Scholl at the Mayo Clinic (2.1 to 1). The incidence in the nonpregnant females was 1:1,100. In this same period of time, 9,882 women were admitted to the white and colored obstetric services of Charity Hospital. Twelve proved cases of renal or ureteral calculi were noted in this group, an incidence of 1:820. The Chicago Lying-in Hospital incidence was 1:900. The combined incidence of renal and ureteral calculi in pregnant patients at the Charity Hospital of Louisiana and the Chicago Lying-in Hospital was 1:852.

From the foregoing, it appears that the frequency of calculous disease of the upper urinary tract associated with pregnancy (1:852) is somewhat greater than in nonpregnant women (1:1,100) but not as

great as in the male (1:320). Unfortunately, we have no comparable statistics from other obstetric clinics.

We do not believe, however, that an incidence presently reported represents the true incidence of lithiasis in pregnancy. More serious attempts at diagnosis would undoubtedly reveal a far greater number of cases. These cases have remained undiagnosed in the past, because adequate diagnostic methods were not employed.

The greater relative incidence of pyelonephritis of pregnancy frequently overshadows the consideration of renal and ureteral calculi. The possibility of stone often does not enter the pale of clinical impression until the patient fails to improve with the numerous agents prescribed to combat infection. Finally, a roentgenogram is made and a calculus is observed in the kidney or ureter or both.

*Race, Age, and Parity.*—Racial comparison is possible only in the 12 cases from Charity Hospital, of which 9 were white and 3 colored patients. The proportional racial distribution is actually greater than three to one, because during the period in which these cases occurred the relative distribution of white and colored obstetric admissions to the hospital was 33 to 67. The reason for this very considerable predilection for the white race is not clear, but it furnishes still another example of the marked variation in medical reaction between the two races.

The age range in the 20 cases was 19 to 43 years, and the average age was 28 years. Although there was a definite preponderance of incidence in the third decade (13 cases) as compared with the older age groups (6 cases), this difference could not be regarded as significant in such a small series.

In regard to the factor of parity, the multiparas (14 cases) exceeded the primiparas (6 cases). Twelve patients, 60 per cent, had had three or more pregnancies, and the average parity was 3.8. In the light of the etiology of urinary calculi previously described, these figures may be regarded as logical findings, inasmuch as pyelectasis and ureterectasis and potential infection are more frequent in women who have had several pregnancies. It is interesting to note in connection with this point, however, that the incidence of calculous disease was no higher in women who had numerous pregnancies as compared with those individuals who had relatively fewer pregnancies. It is not felt, however, that a definite conclusion can be formulated in this paper regarding the relation between the degree of multiparity and incidence of renal and ureteral calculi.

*Duration of Gestation.*—In one case the diagnosis was not established until the second post-partum day; the period of gestation in the others varied from six to forty weeks, the average was twenty-four weeks. Although the range is great it is perhaps significant that 50 per cent of the cases were less than midterm and that symptoms had persisted for several months in most of the cases who remained undiagnosed until late in pregnancy.

*Clinical Features.*—The predominant findings in the descending order of their incidence were costovertebral angle pain and tenderness, abdominal pain and tenderness, fever, pyuria and hematuria, and nausea and vomiting. Less frequently encountered findings were frequency of urination, burning on urination, chills, and muscle spasm. In one case a palpable mass could be demonstrated.

Pain was present in all cases and was usually the chief complaint for which the patients sought relief. The pain varied in intensity but

usually was a constant dull ache in the costovertebral angle of the involved side. Twelve of the patients had attacks of renal colic, but only three suffered excruciating pain. None of the patients had had a previous diagnosis of urinary stone although one had had several attacks of colic before she became pregnant, and a diseased gall bladder had been suspected.

The duration of symptoms also showed great variation. The average patient had experienced complaints for a period of about eight weeks, but some had had symptoms for as long as six months while others had been ill for only one week. The clinical picture usually began with symptoms suggestive of pyelitis but the patient often did not seek



Fig. 1.—E. M. (L-41-46439), 31 years old, white female, gravida iii, was admitted to Hospital on second post-partum day with high fever, chills, and severe pain in right costovertebral angle and right lower quadrant. KUB, large right ureteral calculus and hydronephrosis. Ureterolithotomy performed. Uneventful convalescence.

relief until pain was a predominant feature. As we have stated previously, it is of interest to note that medical consultation was delayed until late in pregnancy in a number of cases, although symptoms had existed since the first trimester.

No unusual or unexpected observations were obtained from the laboratory studies. There was no appreciable azotemia except in three cases (urea nitrogen: 42, 26, and 25 mg. per cent). Thirteen patients had notable amounts of microscopic pyuria and 12 had considerable microscopic hematuria, but only 3 cases had gross hematuria. *Escherichia coli*, staphylococci and streptococci were found on smear and culture of the urine,

The calculi were located in the kidney in 11 cases, in the ureter in 6, in both kidneys in 1, in both ureters in 1, and in both kidneys and both ureters in 1 case. Stones were found on the right side in 12 cases, on the left side in 5, and on both sides in 3 cases. The marked preponderance of stone on the right side corresponds to the increased incidence of pyelitis on that side, and both may be due to the fact that a more marked physiologic dilatation occurs in the right ureter and kidney pelvis than on the left side. It is possible that the changes may be ascribed to the shortened right ureter, its difference in relation to the large iliac and uterine vessels or to dextrorotation of the uterus; all of which tend to increase angulation and occlusion of the ureter.



Fig. 2.—M. M. (L-41-45543), 22 years old, white female, primigravida, was admitted to hospital in the fifth month of gestation, complaining of right costovertebral angle pain, urinary frequency and hematuria of three months' duration. *KUB*, right staghorn calculus. Nephrectomy. Uneventful convalescence.

The site of predilection seemed to be in the uteropelvic junction or in the terminal one-third of the ureter, where it occurred in all 20 cases. A single stone was found in 15 of the 17 cases in which one site only was involved.

#### DIAGNOSIS

The differential diagnosis of calculous disease in pregnancy offers considerable difficulty at times and the percentage of error is high.

This is not unexpected inasmuch as the symptoms and findings closely simulate those of other diseases. In this series only five of the 20 cases were diagnosed correctly on the strength of the clinical picture on admission. In 12 cases, 60 per cent, the tentative diagnosis of pyelitis or pyelonephritis of pregnancy was made; two cases were diagnosed as possible appendicitis. Acute salpingitis, threatened abortion and ectopic pregnancy were also included in some of the clinical impressions.



Fig. 3.—I. A. (T-41-48509), 38 years old, white female, gravida x. Diagnosis on admission: pyelonephritis with block, pregnancy (26 weeks). Further study revealed a right renal calculus. Nephrostomy and nephrolithotomy were performed. Premature infant was born three days later, and died on eighth day. Patient recovered after a stormy convalescence.

There are five avenues of approach to the determination of the presence of urinary calculi:

1. History
2. Physical examination
3. Laboratory studies
4. Cystoscopy
5. Roentgenographic observations

There is usually a history of pain that commences posteriorly over the affected kidney or ureter and radiates around the loin to the labia or lower abdominal quadrant on the same side. Occasionally, the pain may begin in the anterior upper abdominal quadrant of the affected side. The pain varies from a severe lancinating type that may be suf-

ficiently marked to produce prostration to a persistent, dull aching pain especially noted in the chronic cases. These attacks of pain are often associated with nausea and vomiting. A history of hematuria, pyuria, and passage of sand, gravel, or tiny stones is helpful in suggesting the diagnosis. Fever and chills are present as a rule only in the presence of infection.

On physical examination, tenderness over the costovertebral angle may frequently be elicited. Tenderness can also be noted on palpating the kidney. Muscle spasm is not a consistent sign. The kidney may be enlarged due to a persistent block with subsequent hydronephrosis.

Examination of the urine will reveal the presence of red and white blood cells and a variable degree of albuminuria, depending on the amount of blood present in the urine. It is important to remember that there may be no pathognomonic urinary findings in the presence of a complete block.

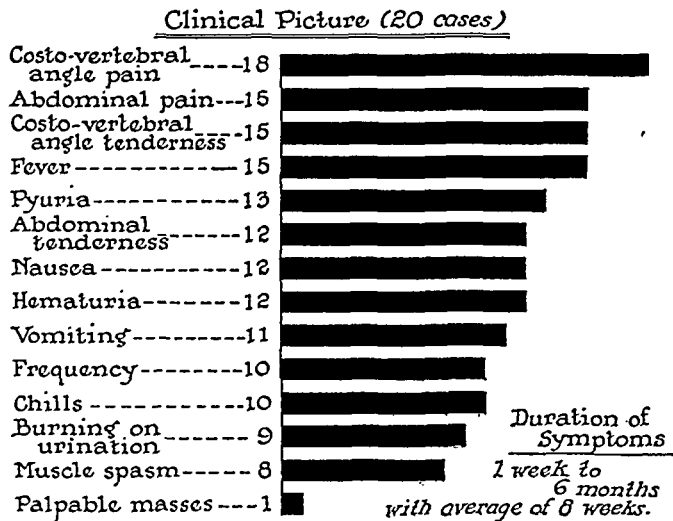


Fig. 4.

Cystoscopic examination can be of inestimable value. Bloody or purulent urine may be noted, being ejected from the ureteric orifice on the involved side. Block and spasm, when encountered while attempting to introduce a catheter up the ureter, are significant in suggesting the presence of a stone.

Three forms of roentgenographic study are available for diagnostic purposes, namely, a plain roentgenograph of the urinary tract, an excretory urogram, and a retrograde pyelogram. The first two procedures do not require cystoscopy and are often preferred for that reason.

TREATMENT

In this series, one or more cystoscopic examinations were performed on each of the 20 patients. The procedure was done once in 14 cases, twice in 4 cases, and three times in 2 cases. Cystoscopic manipulations



were successful in removing the stones in 5 cases, and in 6 additional cases the stones were passed spontaneously after intervals of from one day to five months following cystoscopy.

Nine patients were submitted to major surgical procedures which included ureterolithotomy (3 cases); nephrectomy (2 cases); nephrolithotomy, pyelolithotomy, nephrostomy, and combined ureterolithotomy and nephrostomy (each one case). Six operations were performed during pregnancy; while in three cases, surgical intervention was deferred until after delivery. One of the latter cases required nephrectomy, and it appeared likely that earlier intervention possibly would have spared the kidney.

Specific chemotherapy was employed whenever possible, especially in the administration of the sulfonamides and mandelates. Supportive measures consisted of fluids by mouth, infusions, transfusions, wholesome diets, and pure vitamin principles. Indwelling ureteral catheters were employed to enhance drainage as indicated. Labor was induced once.

The only specific suggestion that is suitable in governing the treatment of urolithiasis in pregnancy is that each case requires individual appraisal and judgment. One must not lose sight of the fact that the approach to the problem must be directed toward a threefold objective, namely, preservation of the life and well-being of the mother, the fetus, and the kidney on the affected side. Toward this end, a few basic criteria should be kept in mind. Briefly, these may be outlined as follows:

1. The size of the stone
2. The location of the stone
3. The presence of infection
4. The duration of symptoms
5. The efficiency of renal function on the unaffected side
6. The status of the patient (toxemia, azotemia, etc.)
7. The period of gestation

A routine that allows wide latitude of variations and modifications is suggested, based on the assumption that the diagnosis of urinary calculi has already been made. In the Charity Hospital of Louisiana, a similar systematic follow-up is conducted in close cooperation by the obstetric and urologic services.

#### I. SYSTEMIC CARE

##### A. *Fluids.*—

1. Fluids are forced by mouth (3,000 c.c. daily minimum). The intake and output should be carefully charted by the nursing staff. During the summer months or if the patient has a tendency to perspire profusely, an extra 1,000 c.c. of fluid is given.

2. In the presence of marked vomiting or when the patient refuses to take adequate fluids by mouth, 3,000 c.c. of fluid are given by infusion distributed as follows: 1,000 c.c. of 10 per cent dextrose in normal saline; and 2,000 c.c. of 10 per cent dextrose in distilled water.

3. Blood transfusions as necessary to combat anemia.

*B. Urinary Antiseptics.*—These are prescribed according to the type of organisms found on smear and culture of urine.

1. Staphylococci: sulfathiazole, sulfadiazine, neoarsphenamine.
2. Streptococci: sulfanilamide, sulfadiazine.
3. Bacillary infections: mandelates.

*C. Sedation.*—It is important to keep the patient comfortable, but it is equally essential not to maintain the patient in a stuporous state. The choice of hypnotics should be influenced by the fact that these are being administered to a pregnant individual.

*D. Urinary Suppression.*—

1. Diathermy over each kidney for twenty minutes, every four hours.
2. Sucrose (50 per cent), 50 c.c., intravenously, B.I.D.
3. Caffeine sodium benzoate, gr. VISS, T.I.D.
4. Fluids as prescribed above.
5. Ureteral catheterization as indicated.

## II. TREATMENT OF THE OFFENDING CALCULI

### *A. Renal Calculi.*—

1. In the absence of infection and complete block, conservative measures are justified. Supportive measures should be sufficient in most instances and specific treatment (nephrolithotomy, nephrectomy, etc.) postponed until a future propitious postpartum date.

2. In the presence of infection, treatment should be aimed at combating this factor (fluids, chemotherapy, etc.). In the presence of a block, it is mandatory that drainage be established by means of an inlying ureteral catheter or even a nephrostomy. Sometimes a small stone will pass spontaneously or with the aid of antispasmodics and catheter manipulation. It should be emphasized that surgical measures should be contemplated if appreciable improvement is not attained by conservative means within a reasonable length of time. This may take the form of nephrolithotomy, pyelolithotomy, or even nephrectomy. Jones<sup>11</sup> has reported a case of pyelonephritis of pregnancy complicating bilateral renal calculi in which a right nephrectomy and left nephrolithotomy were done.

### *B. Ureteral Calculi.*—

1. In the absence of infection and complete block, conservative measures are indicated (sedation, antispasmodics, etc.).

2. In the absence of infection, but in the presence of a complete block, the primary consideration is to re-establish drainage. This is accomplished by means of introducing a ureteral catheter proximal to the site of obstruction.

After drainage is established, an attempt should be made to dislodge the calculus by means of ureteral manipulation, antispasmodics, etc. If it is not possible to get by the site of obstruction with a catheter after a reasonable number of trials, a ureterolithotomy should be contemplated. It is also important to prescribe prophylactic measures in anticipation of any potential infection.

3. In the presence of infection, drainage must be assured. Specific measures must be taken against the infection and the calculus should ultimately be removed. Surgical measures should be performed as indicated.

It is needless to analyze each of these points in definite detail. The significance of most of them is self-evident and the numerous varia-

tions encountered need not be completely enumerated in this paper. The final decision will remain within the province of discussion and judgment of the obstetrician and urologist acting in mutual collaboration.

A few salient points should be borne in mind in connection with the above routine. For instance, a small stone, which ordinarily would pass without any appreciable difficulty might become imbedded with stubborn resistance at any of the several normal sites of constriction in the ureter. The complete obstruction that might result in this situation is fraught with no less danger than a much larger calculous formation in the kidney. It is more encouraging to deal with a stone that has passed half way down the ureter than one which meets an impasse at the ureteropelvic junction; in the former case, we have more reasonable assurance that the stone might pass spontaneously or with the aid of antispasmodic drugs and catheter manipulation.

There may be fortunate occasions during which one can afford to temporize such as when drainage can be re-established by means of an inlying ureteral catheter, infection is controlled, and excellent renal function is present on the unaffected side. At other times, surgical interference may be indicated, such as in the case of an uncontrolled infected hydronephrosis complicating calculous obstruction. When surgical intervention becomes the treatment of choice, pregnancy and parity should be secondary considerations.

Frequently, especially early in pregnancy, there is a reluctance to subject the pregnant patient to cystoscopic examination and ureteral catheter manipulations for fear of exciting abortion or premature labor. Our own experience has led us to conclude that this attitude is not justifiable. We have found that these urologic procedures can be performed as frequently as indicated, providing that proper sedation and utmost gentleness are put to use. In connection with this point, the following findings are of interest. In the interval between July, 1940, and July, 1941, 106 patients with pyelonephritis of pregnancy were admitted to the Charity Hospital. Of this number, 35 patients received cystoscopic examinations. Two of this group of patients, both near term, went into labor and delivered normal viable babies within twenty-four hours of the cystoscopy. It would be difficult to evaluate the part played by the urologic procedure in stimulating labor. In this series there were no other instances of premature labor initiated by the cystoscopic procedure, and there were no accidents or untoward effects.

#### RESULTS

There was no maternal mortality. There were 3 fetal deaths, an uncorrected fetal mortality of 15 per cent. L. L., six weeks pregnant, required a pyelolithotomy; abortion occurred on the seventh postpartum day. N. A., twenty weeks pregnant, passed a ureteral stone

following cystoscopy, but aborted forty-eight hours later. I. A., eight months pregnant, required a nephrostomy and nephrolithotomy and delivered a premature baby who died eight days later. In three other cases premature delivery occurred, but the infants survived.

#### SUMMARY AND CONCLUSIONS

1. Twenty cases of nephrolithiasis or ureterolithiasis complicating pregnancy are reported, with no maternal deaths and a gross fetal mortality of 15 per cent. In this series the incidence of urolithiasis was one in every 852 pregnancies, which is about twice the frequency found in nonpregnant females of the same age group. Only 3 occurred in colored patients.

2. Race, sex, age, endocrine factors, and vitamin and mineral metabolism play a part in stone formation, but the chief causes, apparently, are stasis and infection. Pregnant women undoubtedly present a number of cardinal requisites for calculous formation but these are counteracted in part by the fact that pregnancy is of relatively short duration.

3. The clinical features of urolithiasis associated with pregnancy are briefly discussed. The diagnosis is dependent upon the demonstration of the stone, which is most readily identified by cystoscopic and roentgenologic examinations.

4. Pyelonephritis is easily confused with urolithiasis during pregnancy, and 12 of 20 cases were so diagnosed. The close clinical similarity of the two conditions is responsible for the error.

5. Lumbar pain and tenderness, fever, and nausea and vomiting were the outstanding symptoms; the chief laboratory findings were pyuria and hematuria.

6. In general, the management of urolithiasis during pregnancy depends upon the individual case, and a high degree of obstetric and urologic cooperation is demanded. If the condition is latent or the symptoms not severe, conservative therapeutic measures are preferable. After parturition the stone should be removed. In those cases in which symptoms are severe, operation is mandatory. In most instances the pregnancy will continue without interruption. Urethral passage of the stone occurred in 11 cases while 9 cases required surgical intervention.

7. While cystoscopy during pregnancy should not be considered an innocuous procedure, evidence is given in support of the view that its hazards do not contraindicate its use in properly selected cases.

8. Urolithiasis during pregnancy is a condition which demands general recognition and further study. Only by these means will the true incidence be established, the etiologic factors peculiar to pregnancy be determined, and improved methods of diagnosis and treatment be evolved.

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## ADDENDUM

Since this manuscript was prepared, two additional cases of ureterolithiasis associated with pregnancy have been observed in the Charity Hospital at New Orleans. Spontaneous expulsion occurred in one instance, while in the other the stone was removed by means of cystoscopic manipulation. The patients were white multiparas in the second trimester of pregnancy, and the gestations were undisturbed.

## TOXIC MANIFESTATIONS IN THE NEWBORN INFANT FOLLOWING PLACENTAL TRANSMISSION OF SULFANILAMIDE

WITH A REPORT OF 2 CASES SIMULATING ERYTHROBLASTOSIS FETALIS

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THE purpose of the present communication is to describe a hitherto unreported mode of sulfonamide toxicity and to add a further note of caution against the indiscriminate use of the sulfonamides, specifically, during pregnancy. This has been occasioned by the observation of two cases of sulfanilamide toxicity in the newborn, one fatal, following the administration of the drug to the pregnant mother.

In 1937, Marshall, Emerson, and Cutting<sup>1</sup> demonstrated that sulfanilamide is rapidly distributed throughout the body and may be found in somewhat varying concentrations in the different tissues of the body soon after it is administered. Shortly thereafter, it was shown that the drug passes readily through the placental barrier<sup>2</sup> and may be found in the fetus soon after administration to the mother, equilibrium between the concentrations in the fetal and maternal blood being reached in three to five hours. This is true for both man and animal (rabbit, rat). The ready passage of the drug through the placenta apparently does not vary with the stage of pregnancy, thus differing from the passage of neoarsphenamine.<sup>3</sup> There is evidence to show that sulfapyridine, at least, of the other members of the sulfonamide group of drugs, also passes freely through the placenta.<sup>4</sup> The extensive use of sulfanilamide and other sulfonamides during pregnancy for various complicating

intercurrent infections therefore raises the question of the possible deleterious effects of these drugs upon the fetus.

There are only meager clinical reports on the effects of placenta-transmitted sulfanilamide. In a series of 17 cases, Barker<sup>2b</sup> found no complications in any of the infants. However, the doses given were small, varying from 15 to 80 gr. given to the mothers at term, 0 to 40 hours before delivery. Likewise, Speert<sup>2c</sup> found no ill effects on the infants in 15 cases of administration of sulfanilamide to pregnant women. Here again the doses were small and given at term, a single dose of 0.06 Gm. per kilo of body weight one to thirty-eight hours before delivery. In the experimental field, Speert,<sup>4</sup> working with rats, found that prolonged administration of sulfanilamide, in amounts well within the limits of safety to the adult animal, produced markedly injurious effects on the fetus, as demonstrated by increased intrauterine and post-natal mortality, decreased litter size, decreased birth weight, and striking selective stunting among the offspring. As Speert remarks, the selectiveness of the stunting suggests a possible individual idiosyncrasy or sensitization to the drug, a point which will be considered again in the discussion.

It would appear, then, from Speert's observations, that the prolonged administration, during pregnancy, of sulfanilamide and, without doubt, the other sulfonamide drugs, is not without the possibility of danger to the fetus or its postnatal development. Nor does the absence of ill effects on the infants in the above-mentioned clinical reports militate against the possibility of the occurrence of occasional serious toxic effects of the drug in the newborn due to individual hypersensitivity, just as they occur only occasionally in patients to whom the sulfonamides are administered directly. We consider it timely, therefore, to present a case of fatal acute yellow atrophy of the liver in the newborn due to sulfanilamide transmitted from mother to fetus through the placenta, and a case of acute hemolytic anemia in the newborn, with recovery, in which this same mechanism seems probable. We have been unable to find any similar recorded observations. These cases are of further interest, in that, because of the clinical and hematologic features, they were both, apparently erroneously, diagnosed as erythroblastosis fetalis.

CASE 1.—M. W., an 18-year-old primigravida, colored female, was admitted to the Sydenham Hospital Oct. 22, 1940, with ruptured membranes. Other details of the history, physical examination, and laboratory data were not significant, except that the Kahn, Kline, and Wassermann tests were negative. On the second day the temperature rose to 102° F. and on the third to 103.6° F. A diagnosis of infection of the amniotic sac was made, and 15 gr. of sulfanilamide were given every four hours. Seven doses were given, a total of 105 gr. No determinations of blood-level concentration were made. Three hours after the last dose, spontaneous delivery of an apparently normal, healthy female infant took place. On the third day after delivery, the mother's temperature became normal and the subsequent course was uneventful.

The child weighed at birth 4 pounds, 12 ounces and measured 20 inches in length. The color and condition of the infant were good, and physical examination revealed no abnormalities. The temperature was normal for the first three days, but on the fourth day rose to 101.4° F. and, for the first time, the infant appeared icteric and the condition poor. A blood count at this time revealed 13.9 Gm. Hg (82 per cent) per one hundred c.c.; and 3,950,000 erythrocytes, 33,350 leucocytes, and 270,000 platelets per c.mm. Differential smear showed 51 per cent segmented and 20 per cent nonsegmented neutrophilic leucocytes, 2 per cent myelocytes, 22 per cent lymphocytes, and 5 per cent monocytes. The smear also showed polychromasia, and 34 nucleated erythrocytes per 100 leucocytes, megaloblasts predominating. The urine contained a trace of urobilinogen and no bile. The stools were of normal color. The liver and spleen were not palpably enlarged. On the following day, the fifth day of life, a sulfanilamide determination of the blood showed 1.5 mg. per cent, although the child had never been given the drug directly. On October 31, three days after the first count, a second blood count showed 16.5 Gm. Hg, 4,000,000 erythrocytes and 23,950 leucocytes with 51 per cent segmented and 18 per cent nonsegmented neutrophils, 24 per cent lymphocytes, and 7 per cent monocytes; and there were 27 nucleated erythrocytes per 100 leucocytes. The jaundice increased and the child's condition became increasingly poor. She vomited frequently, and became cyanotic at intervals. Except on 2 occasions and terminally, the temperature remained normal. Death occurred a little more than eight days after birth. The final clinical diagnosis was erythroblastosis fetalis.

*Necropsy.—Gross Findings:* The body was that of a poorly nourished, colored female infant, 2,100 Gm. in weight and 48 cm. in length. The sclerae were distinctly icteric, and there was an icteric tint to the rather light-colored skin. Except for a focal, pinhead-sized hemorrhage in the left cerebellum, the macroscopic pathologic changes were confined to the liver. The liver weighed approximately 100 Gm., and was of normal or somewhat diminished size, and of soft consistency. The liver parenchyma was of a mottled brownish-red to yellow color and peppered throughout with innumerable small grayish white dots. The portal and hepatic vessels, gall bladder and bile ducts were normal. The spleen weighed 10 Gm., and was essentially of normal size and gross appearance, and firm in consistency. The umbilical stump was clean. There was no kernicterus of the basal nuclei of the brain.

*Microscopic Findings.—Liver:* Microscopic sections of all portions of the liver showed an extraordinary picture of extensive necrosis with only scattered, irregular islands of intact parenchyma which had no constant relation to the lobular architecture. The preserved liver cells were, for the most part, either histologically normal or showed mild fatty change; they merged either abruptly, or gradually with intervening more or less degenerated cells, with the areas of necrotic parenchyma. Both in the areas of intact parenchyma, including the portal connective tissue, as well as in the degenerated and necrotic areas, there was a complete absence of either intrasinusoidal or interstitial extramedullary hematopoiesis. The necrotic areas constituted the major portion of all sections. They consisted in part of remaining shadows of necrotic "ghost" liver cells and pyknotic nuclear material, and in part of areas where the necrotic liver parenchyma had completely disappeared, leaving only the congested sinusoids and reticulum framework of the liver. No evidence

of any inflammatory reaction was present, and careful search with special stains failed to reveal any bacteria or spirochetes. *Adrenals:* Sections of both adrenals showed numerous focal areas of necrosis of the cortex, very similar in appearance to those in the liver but smaller and less extensive, alternating with completely intact parenchyma. Here also there was a complete absence of bacteria, inflammatory reaction,



Fig. 1.—(Case 1.) Photomicrograph of liver showing extensive degeneration and necrosis of parenchyma. Low power ( $\times 56$ ).

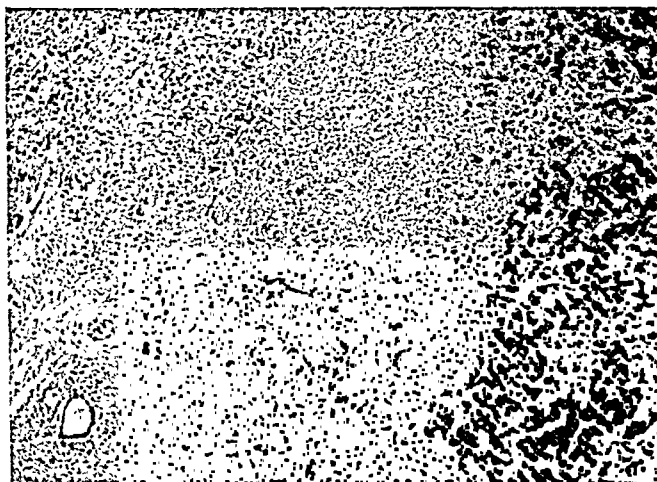


Fig. 2.—(Case 1.) Higher magnification showing details of the liver necrosis and absence of hematopoiesis. ( $\times 96$ )

or hematopoiesis. *Spleen:* Sections showed a normal architecture and structure. The Malpighian corpuscles were of normal size and number. Within the red pulp were scattered, microscopic foci of necrobiosis. There was no evidence of the extramedullary hematopoiesis or myeloid metaplasia, or picture of arrested development of the spleen characteristic of erythroblastosis fetalis.<sup>5</sup> No noteworthy hemosiderosis was present.



Histologic study of the other organs included a section of the lung showing 2 microscopic foci of necrobiosis of the alveolar walls, a section of the left cerebellum showing a small, focal hemorrhage with early perifocal cellular reaction, and sections of the kidney showing mild tubular degeneration. Sections of the bone marrow, studied in detail, showed no significant changes. Sections of the umbilicus and umbilical veins up to the liver showed no evidence of infection.

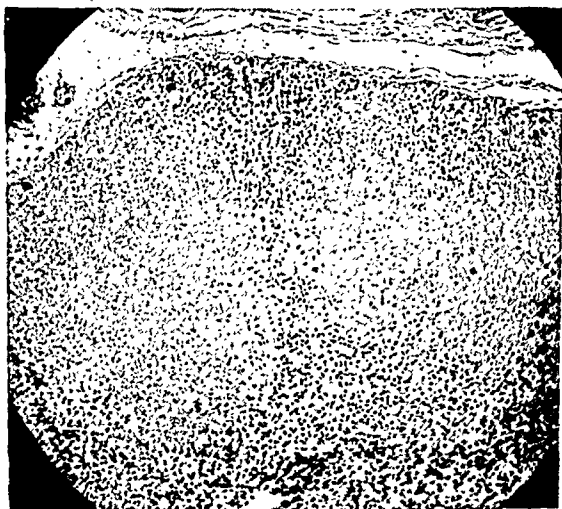


Fig. 3.—(Case 1.) Photomicrograph of adrenal showing areas of cortical necrosis. ( $\times 60$ .)

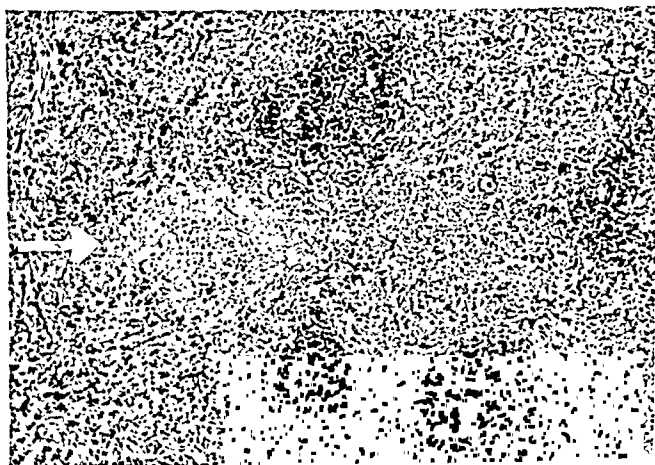


Fig. 4.—(Case 1.) Photomicrograph of spleen showing normal pulp and follicle structure and absence of extramedullary hematopoiesis or myeloid metaplasia. Arrow points to focal area of necrobiosis. ( $\times 96$ .)

#### COMMENT

In the absence of any evidence of bacterial infection, congenital syphilis, or congenital obliteration of the bile ducts, the combination of jaundice and the erythroblastotic blood picture naturally suggested the diagnosis that was made of erythroblastosis fetalis, although, in retro-

spect, the absence of anemia, hepatomegaly and splenomegaly, the onset of jaundice only on the fourth day, and the fact that this child represented the first pregnancy of this mother speak against the diagnosis. In view of the recent studies of Levine and his co-workers<sup>6</sup> on the etiology and pathogenesis of erythroblastosis fetalis, it is unfortunate that the parents are not now available to determine their Rh status. However, the pathologic findings, especially in the liver and spleen, are sufficient to negate this diagnosis and to show instead that the case is one of acute yellow atrophy of the liver associated with focal necroses of the adrenals, spleen, and lung, in which there appears full justification for attributing these changes to the sulfanilamide that was demonstrated in the infant's blood on the fifth day of life and which had been transmitted from mother to infant through the placenta.

CASE 2.—M. C., a full-term, spontaneously delivered, three-and-one-half-week-old, white female infant, was admitted to the Sydenham Hospital Sept. 13, 1940, because of marked pallor since birth and the development of a faintly yellow color in the skin. The child had otherwise been perfectly normal, and one sibling five years old was living and well. It was subsequently learned that the mother had taken 57 tablets of sulfanilamide shortly before delivery, although unfortunately the exact details concerning this medication and the nature of the infection for which the drug was given were not recorded on the infant's chart.

On admission, the blood count showed 6.8 Gm. Hg per 100 c.c. (40 per cent) and 2,020,000 erythrocytes and 8,600 leucocytes per c.mm., with 10 per cent nonsegmented and 21 per cent segmented neutrophils, 1 per cent eosinophils, 60 per cent lymphocytes, and 8 per cent monocytes; there were 41 nucleated erythrocytes per 100 leucocytes. Polychromasia, basophilic stippling, and microcytosis were noted. Reticulocytes were 9.3 per cent. A second count, three days later, showed an essentially similar picture as did a third, two days later, except that the hemoglobin had fallen to 5.6 Gm. and the erythrocytes to 1,590,000. The liver and spleen were moderately enlarged. The indirect van den Bergh gave a result of 1.6 mg. per cent of bilirubin; the direct was negative. The clinical diagnosis was erythroblastosis fetalis.

The child remained in the hospital for two months and was treated by diet with iron and liver, and received 4 small transfusions totaling 215 c.c. of citrated blood. On this treatment the infant made a complete recovery, successive blood counts showing a progressive disappearance of the nucleated erythrocytes, the reticulocytes dropping to 1.2 per cent on Nov. 12, 1940, and the hemoglobin rising to 11.7 Gm.

#### COMMENT

Except for absence of the usual leucocytosis and "shift to the left" of the leucocytes, the clinical and hematologic features in this case justify the diagnosis that was made originally of erythroblastosis fetalis. However, the excellent result effected by a treatment consisting chiefly of 4 small transfusions complemented by small amounts of liver and iron cast some doubt on the correctness of this diagnosis, and, after the

necropsy in the first case, the clinical and hematologic similarities of the two cases were recalled; it was at this time that we felt that this was possibly not a case of erythroblastosis fetalis, but, from the lesson drawn in the first case, might well represent a severe hemolytic anemia due to placenta-transmitted sulfanilamide and such as is not infrequently found to complicate the direct administration of sulfanilamide. It is unfortunate that the exact details of the amounts and time of the administration of the sulfanilamide to the mother, especially in relation to the time of delivery, are not available, and that no sulfanilamide determination was done on the infant. It is unlikely in any case that the latter procedure would have given any information inasmuch as the child was not seen in the hospital until three and one-half weeks after birth.

#### DISCUSSION

The clinical and especially the pathologic evidence in the first case is clearly sufficient to warrant discarding the diagnosis of erythroblastosis fetalis and attributing the fatal liver damage to sulfanilamide transmitted from the mother to fetus through the placenta. The data in the second case are, unfortunately, not so conclusive, but here, also, there appears to be good reason to doubt the diagnosis of erythroblastosis fetalis and consider a similar mechanism responsible for the development of the anemia. This is all the more likely in view of the fact that liver damage, acute hemolytic anemia, and reticulocytosis (as was present in Case 2) have been noted not infrequently following direct therapy with sulfanilamide. It is of interest that the placenta-transmitted sulfanilamide should stimulate such a hematic reaction in these infants, for which two factors, at least, are probably responsible. As shown by Watson and Spink,<sup>7</sup> sulfanilamide causes an acceleration of hemoglobin metabolism characterized by an increase in fecal urobilinogen and a varying increase in reticulocyte percentage, increased hemolysis, and a disturbance in hemoglobin formation as evidenced by the occurrence of macrocytic or normocytic, mildly hypochromic anemia. In addition, it is not unusual for the rather labile hematopoietic process in the newborn to react in this manner to a variety of stimuli, such as infections, anemia, etc., even in the absence of true erythroblastosis fetalis.

The evidence of these two cases demonstrates that the free passage of sulfanilamide through the placenta when given to the pregnant mother exposes the fetus or newborn infant to the hazards of the possible toxic effects of the drug. Inasmuch as sulfapyridine also has been shown to pass through the placenta as freely as sulfanilamide, this danger must be considered possible for all of the sulfonamides. This is pointed out, not with any intention of discouraging the use of these extremely valuable therapeutic agents, but to re-emphasize the caution with which they must be used.

In regard to sulfanilamide specifically, the most grave of the toxic effects include acute hemolytic anemia, leucopenia and neutropenia, and more or less severe or even fatal liver damage. The last, contrary to the supposition of many, is by no means uncommon, and was the obvious cause of death in Case 1.

Watson and Spink<sup>7</sup> observed 16 cases of distinct or marked jaundice in 110 patients receiving sulfanilamide, although the latter figure did not include all the patients receiving the drug, making the actual incidence of the complication uncertain. Long, Bliss, and Feinstone<sup>8</sup> report 2 cases of jaundice without anemia clearing rapidly on withdrawal of the drug among 307 adults treated. Other cases of liver damage with recovery have been reported by Hageman and Blake,<sup>9</sup> Saphirstein,<sup>10</sup> Garvin,<sup>11</sup> Silver and Elliott,<sup>12</sup> Fitzgibbon and Silver,<sup>13</sup> Greene and Hotz,<sup>14</sup> and Spring and Bernstein;<sup>15</sup> fatal cases by Garvin,<sup>11</sup> Bannick, Brown, and Foster,<sup>16</sup> and Ottenberg;<sup>17</sup> and fatal cases with post-mortem demonstration of liver damage by Greene and Hotz,<sup>14</sup> Tragerman and Goto,<sup>18</sup> Russell<sup>19</sup> (neoprontosil also given), Berger and Applebaum,<sup>20</sup> and Cline.<sup>21</sup> In the last 3 reports, as also in our Case 1, the liver changes described were of the order of an acute or subacute yellow atrophy of the liver.

Acute hemolytic anemia, as evidenced in our Case 2, is an even more common manifestation of sulfanilamide toxicity in patients to whom the drug is given directly.

Long, Bliss, and Feinstone<sup>8</sup> noted the common occurrence of a mild type of anemia, and an incidence of a more severe, acute hemolytic anemia in 2.9 per cent of 307 adults and 8.9 per cent of 101 children treated. Wood<sup>22</sup> reports an incidence of acute hemolytic anemia in 2.4 per cent of 378 adults and 8.3 per cent of 144 children following the use of the drug. Numerous individual case reports of acute hemolytic anemia due to sulfanilamide have been recorded which need not be tabulated here. This complication may be explained by the acceleration of hemoglobin metabolism and disturbance in hemoglobin formation referred to above.

The mechanism of the liver damage induced by sulfanilamide cannot be explained so satisfactorily. A number of authors,<sup>8, 12-14, 16, 20, 29</sup> on grounds which are not certain, believe that it may either be due to individual idiosyncrasy or be based upon an allergic or sensitization mechanism as with arsphenamine, cinchophen, and aminopyrine. In connection with the latter suggestion, it is a curious fact that, in a number of cases,<sup>11-13, 17, 20, 21</sup> treatment was interrupted and the evidence of liver damage developed soon after resumption of the drug; in some of these cases, symptoms of milder toxicity were present with the first course of treatment. This would suggest the possibility that in these cases an allergic mechanism in a sensitized patient was responsible for the damage. Goldman, Applebaum, and Antopol<sup>23</sup> made a similar observation in respect to cases of malignant neutropenia following the use of sulfapyridine, as did Rosenthal and Vogel,<sup>24</sup> and Volini and others<sup>25</sup> noted that sensitization may follow resumption of interrupted medication with sulfathiazole. Kracke and Parker<sup>26</sup> have dis-

cussed at some length and cited evidence in favor of an allergic mechanism of certain drug reactions. This possibility, in the case of sulfanilamide, is further suggested by a very interesting case reported by Salvin<sup>27</sup> of a 22-year-old male who, after 4 doses of 10 gr. each of sulfanilamide, developed intense, generalized itching accompanied by sneezing, shortness of breath, lacrimation, swelling of the eyelids, lips, and scrotum, and urticaria-like lesions of the face, ears, inner margins of elbows and knees, and the abdomen. The sulfanilamide was discontinued, a large dose of magnesia magma was given, and 3 drops of epinephrin administered subcutaneously; this treatment was followed by disappearance of the symptoms. Patch tests with sulfanilamide, but not with other related compounds, produced a positive reaction. A repeat dose of 1 gr. of the drug brought on a similar attack.

A similar case was reported by Schonberg<sup>28</sup> of a 21-year-old woman who was given 20 gr. of sulfanilamide every six hours on the first day, and 10 gr. every six hours thereafter for a vulvar infection. On the fourth day she developed a generalized erythematous eruption composed of wheals and macules. After an interval of one month, a single dose of 5 gr. of the drug was followed by a generalized scarlatiniform erythema with intense pruritus, acute edema of the eyelids, lips, larynx, and forehead, considerable difficulty in breathing, and pain in the chest.

Davidson and Bullowa<sup>29</sup> have listed a number of such cases in the literature which they consider examples of true acquired hypersensitivity to sulfanilamide. In these cases, "a reaction, usually chills, fever and a rash, occurred during treatment after the patient had already received a substantial amount of the drug, and was reproducible later by the administration of a small amount of sulfanilamide."

The suggestion of individual drug idiosyncrasy in some cases is supported by the observation of a number of cases in which evidence of liver damage has developed after the administration of small amounts of sulfanilamide. This mechanism was evident in a recent case observed by one of us of a 34-year-old physician, who, after a single dose of 30 gr. of sulfanilamide by mouth for an acute infection of the epiglottis, developed severe jaundice with an icteric index of 96 which cleared readily under appropriate treatment.

#### SUMMARY

Sulfanilamide (and probably also the other sulfonamides) passes through the placenta when given to the pregnant mother and is soon present in the blood and tissues of the fetus in concentrations equal to those in the mother. This would appear to expose the fetus and newborn to the hazards of the possible toxic effects of these drugs. We report a case of acute yellow atrophy of the liver associated with necroses in other organs in a newborn infant following administration to the mother of sulfanilamide which was found in the infant on the fifth day of life in a concentration of 1.5 mg. per cent. We also report a case of acute hemolytic anemia in a newborn infant probably but not certainly due to the same mechanism. The clinical and hematologic features in

both cases suggested the apparently erroneous diagnosis of erythroblastosis fetalis.

The mechanism of the anemia following sulfanilamide administration appears to be an acceleration of hemoglobin metabolism and a disturbance in hemoglobin formation, in addition to increased hemolysis. It is suggested that other toxic reactions due to sulfanilamide may be based either upon individual idiosyncrasy or upon an allergic or sensitization mechanism.

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NOTE: The following apparently relevant paper is listed in the Quarterly Cumulative Index 29: p. 234, but was not available in the library of the New York Academy of Medicine.

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## CYCLICAL ESTROGEN THERAPY\*

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WITH the release of diethylstilbestrol for general use, there is need for emphasizing certain principles of estrogenic therapy that were not so important when we were limited to the use of less potent and more expensive estrogens. Besides untoward side effects peculiarly related to the gastrointestinal tract, the exact nature of which is not understood, there are other conditions that may be and have been produced and that can and should be avoided. Ovulation and menstruation can be inhibited, endometrial hyperplasia can be produced, uterine bleeding of abnormal character and profuseness may be induced, and refractoriness to the benefits of estrogen therapy in general may be developed. All of these untoward effects of diethylstilbestrol therapy may be avoided by the judicious use of *cyclical* estrogen therapy. The use of estrogens in obstetrics and their administration by inunction and the intravaginal route have been omitted from this discussion.

Long term experiments in rats and mice, which have received pellets of estrogens, unesterified estrogens daily, or estrogen esters less frequently for several weeks or months, have revealed the harmful and toxic effects of uninterrupted treatment. Growth and gain in weight have been inhibited, premature epiphyseal closure has been effected, pyometra and death due to septicemia and hepatic and renal cloudy swelling and necrosis have occurred. Metaplasia, adenoma, and carcinoma of the reproductive organs have been produced (Lacassagne,<sup>1</sup> 1935; Loeb and others,<sup>2</sup> 1936; McEuen,<sup>3, 4</sup> 1936; Freudenberg and Clausen,<sup>5, 6</sup> 1937; Gardner and Allen,<sup>7</sup> 1937; Perry and Ginzton,<sup>8</sup> 1937; Zondek,<sup>9</sup> 1937; Gardner and others,<sup>10</sup> 1938; Gaarenstroom and Levie,<sup>11</sup> 1939; Kochakian,<sup>12</sup> 1940; Russell and others,<sup>13</sup> 1941; Page and others,<sup>14</sup> 1941).

Aplastic anemia has been produced in normal dogs of both sexes and in ovariectomized dogs after treatment with large doses of estrone, estradiol benzoate, and diethylstilbestrol (Tyslowitz and Dingemans,<sup>15</sup> 1941).

Lipschütz and others<sup>16</sup> (1941) have demonstrated the toxic effects on guinea pigs of prolonged treatment with estradiol monobenzoate under different timing conditions. Thus, a given quantity of estrogen administered over a period of sixteen weeks produced hyperplasia, polyps,

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fibroids, and bleeding, while many times the dose administered over a longer period of time but with frequent intervals without treatment did not produce these untoward effects. Schilling and Laqueur<sup>17</sup> (1941) have shown that continuous treatment of thyrohyperplastic rats with estrone has produced a significant increase in the weight of the pituitary while intermittent doses ten times as large but administered at ten-day intervals did not affect the pituitary to a degree that was statistically significant.

Cyclical estrogen therapy, on the other hand, has produced no such untoward effects. In this laboratory, where several thousand mice have been used for estrogen bio-assay, many of them for periods of six to twelve months, the mortality among test animals does not differ significantly from that of the rest of the animal colony. In spite of the fact that each animal receives a dose of estrone of from 0.2 to 2.0 micrograms or equivalent urinary estrogen once each week (cyclically), genital tumors and pyometra have not occurred.

The problem of dosage of estrogens may be of utmost importance from the standpoint of degree of effectiveness of the hormone on the organism. Selye<sup>18</sup> (1940) has reported an acquired resistance to estrogen overdosage without antihormone formation. His conclusions were based on experiments on rats receiving prolonged daily treatment with estradiol and diethylstilbestrol. Thus he showed by means of weight curves that "animals, which following an initial state of weight loss, had adjusted themselves to the treatment sufficiently to gain weight in spite of continued treatment, eventually lose weight again and finally die. . . ." Experiments are in progress in this laboratory which show by other criteria the development of a refractoriness to estrogen in the rhesus monkey when treatment is continued over a long period of time without interruption. The method of continuous treatment was by hormone pellet implantation in this study.

In a recent paper (Palmer and Dow,<sup>19</sup> (1941), it was shown that cyclical estrogen therapy to mice with *threshold* doses of estrone provoke the greatest possible reactivity to subsequent estrone treatment. Thus a positive correlation between past and present estrogenic response to threshold doses of estrone has been demonstrated. Decreased sensitivity to estrone appears to follow treatment with doses well below or well above threshold doses.

Bishop and McKeown<sup>20</sup> (1941) have reported that doses of estrone which by daily injection produce continuous estrus in ovariectomized mice did so for short periods only and had to be followed by gradually increasing doses in order to maintain a state of continuous vaginal cornification. Zuckerman<sup>21</sup> (1941) in his experiments on artificial menstruation has observed a definite effect of previous on subsequent responses of rhesus monkeys to estrogens. His observations on subhuman primates appear to have clinical bearing.

The undesirable effects of prolonged estrogen administration to human beings have been reported by Zondek<sup>22</sup> (1940). The normal ovarian



cycle has been inhibited with the production of amenorrhea for seventy days by the injection of 70,000 I.U. of estradiol benzoate. Zondek has produced cystic glandular hyperplasia of the endometrium, inhibited corpus luteum formation, and stimulated adenomatous (eosinophilic) hyperplasia of the anterior lobe of the pituitary. I have observed complete inhibition of menstruation for as long as two cycles in several patients taking 1 mg. of diethylstilbestrol daily for that period of time.

The ease with which cyclical bleeding can be produced in patients with primary amenorrhea along with the development of secondary sex characteristics using threshold doses of diethylstilbestrol cyclically has been reported (Palmer,<sup>23</sup> 1941). Adequate estrogen dosage has been particularly expedient in controlling abnormal uterine bleeding. The rationale for such therapy has been discussed in a previous publication (Palmer,<sup>24</sup> 1941).

Hamblen and others<sup>25</sup> (1941) advocate cyclical estrogen and progestogen therapy in young women with menometrorrhagia and have administered a total of 217 cycles of such treatment to 51 patients. Surgery and radiation procedures have been obviated in their series. Cyclical estrogen therapy has been recommended by MacBryde and others<sup>26</sup> (1941), who have treated 202 women with estrogen deficiency. Their series consisted of women with natural or artificial menopause and young women with amenorrhea and primary hypogonadism. They have found that from 0.3 to 0.5 mg. diethylstilbestrol daily for two to three weeks is an adequate monthly requirement and that the incidence of nausea is 8.6 per cent on interrupted treatment as compared with 20 per cent on continuous treatment.

The means at our disposal for determining the therapeutic dose of an estrogen are rather limited. Therapeutic dosage can be ascertained by the relief obtained from symptoms in menopausal patients, histologic changes in the endometrium, and changes in the vaginal pH and vaginal smear. Insufficient dosage is judged by incomplete relief of symptoms of the menopause, failure of significant lowering of the vaginal pH, inadequate change in the vaginal smear or inactivity in the endometrium. Overdosage, on the other hand, cannot be judged by over relief of symptoms or by changes in the vaginal pH or vaginal smear. Overdosage can, however, be detected by the production of hyperplasia of the endometrium. Wenner and Joël<sup>27</sup> (1939), Wenner<sup>28</sup> (1940), and Palmer<sup>23</sup> (1941) have determined the therapeutic dose of diethylstilbestrol to be in the neighborhood of 40 to 50 mg. per cycle, using the endometrium as the indicator of adequate but not excessive dosage. This amount of estrogen in the case of diethylstilbestrol is greatly in excess of that amount reported by practically all observers for the relief of menopausal symptoms. There is obviously a wide variation in therapeutic dosage of estrogens. When the attempt, however, is being made to produce tissue growth, such as is desired in genital in-

fantilism, and failure in the development of secondary sex characteristics in the female, it is logical to pursue a course by which the most marked effects can be produced without fear of overdosage.

Occasionally it has been observed that the vaginal mucosa, endometrium, and mammary tissue are refractory to estrogenic hormone. It is not unlikely that this refractoriness may account to some degree for the failure of development of these tissues in individuals with primary amenorrhea and genital infantilism, thus accounting for the apparently large doses of diethylstilbestrol required for their development. The

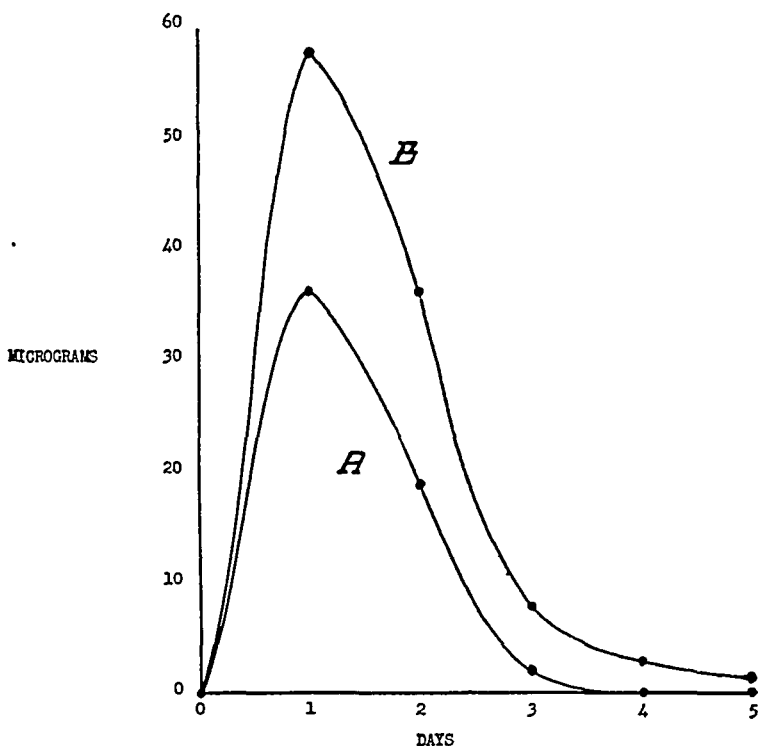


Fig. 1.—Estrogen excretion following a single intramuscular injection of diethylstilbestrol in oil. *A*, after 1 mg., *B*, after 2 mg. (Composite curves compiled from our data and that of Mazer and others, 1941; estrogen in terms of estrone equivalent.)

menopausal woman, on the other hand, has experienced a reproductive period in her life, and for her the therapeutic dose of estrogen is likely to be less, probably in the neighborhood of 0.3 to 0.5 mg. per day. This is offered in argument for the view that the therapeutic dose of diethylstilbestrol varies widely, depending upon the purpose for which the hormone is intended.

We carried out estrogen recovery experiments to compare the excretory level of estrogen of individuals without any ovarian function but who had received diethylstilbestrol, with that of the normal woman, and to determine the proper spacing of diethylstilbestrol administration. In Fig. 1 there are composite curves that show the daily estrogen

excretion following a single intramuscular injection of 1 and 2 mg. (Curves A and B, respectively), of diethylstilbestrol. It can be seen that "peak" excretion occurs during the first twenty-four hours after the intramuscular injection of a dose of diethylstilbestrol. Fig. 2 shows the theoretical type of intermittent estrogen excretion that may be expected by a patient given weekly injections of 1 mg. diethylstilbestrol. Fig. 3 shows estrogen excretion curves compositely compiled from Mazer's<sup>29</sup> data (1941), associated with daily oral administration of diethylstilbestrol. The relative constancy with which the excretory

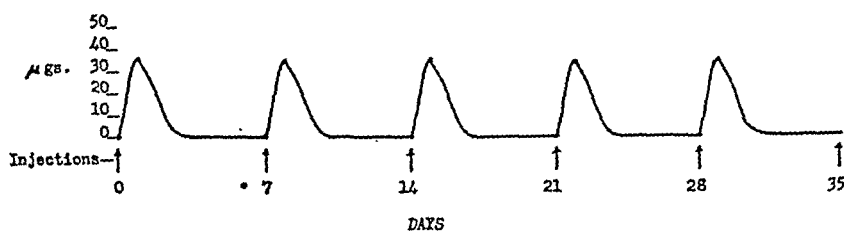


Fig. 2.—Theoretical estrogen excretion following intramuscular injections of 1 mg. diethylstilbestrol at weekly intervals. (Elaborated from Curve A, Fig. 1.)

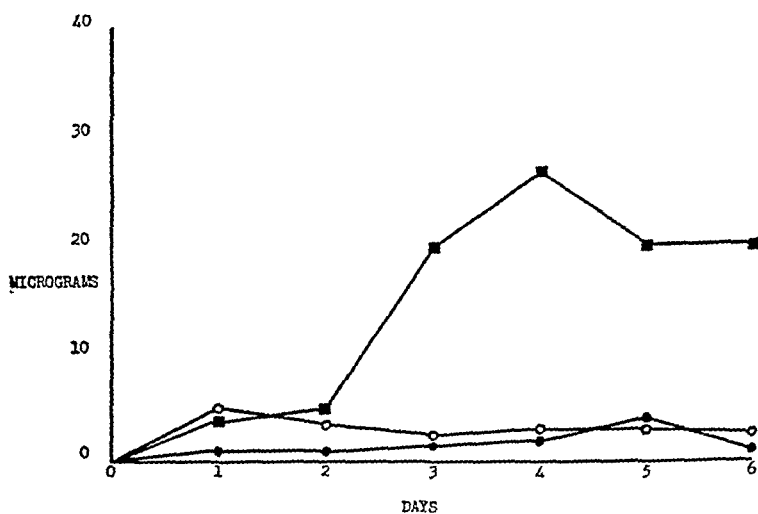


Fig. 3.—Estrogen excretion following daily oral administration of diethylstilbestrol; ●, 0.1 mg. daily; ○, 0.2 mg. daily; ■, 0.5 mg. daily. (Composite curves compiled from the data of Mazer and others, 1941; estrogen in terms of estrone equivalent.)

level of estrogen is maintained when diethylstilbestrol is administered daily by the oral route is obvious. The average daily excretion of estrogen by a normal woman has been found to be 12 micrograms (estrone equivalent) with the range of excretory values being 4 to 30 micrograms per day (Palmer,<sup>30</sup> 1937).

As far as excretory studies are concerned, 40 to 50 mg. of diethylstilbestrol per cycle, as used for the production of anatomic changes in an individual, is associated with an excretion of estrogen greatly in excess of that of the normal woman. Thus the daily administration of

from 0.2 to 0.5 mg. of diethylstilbestrol is followed by estrogen excretion that is comparable to that of the normal woman. It is on this basis that we recommend the therapeutic dose of diethylstilbestrol for the relief of menopausal symptoms to be in the neighborhood of 0.2 mg. to 0.5 mg. per day. The dose of other estrogens that may be used can be determined from Table I.

TABLE I. APPROXIMATE AMOUNTS (MICROGRAMS) OF VARIOUS ESTROGENS REQUIRED TO PRODUCE ESTRUS IN 50 PER CENT OF GROUPS OF OVARECTOMIZED MICE (EMMENS,<sup>35</sup> 1938)

| ESTROGEN<br>(1)     | BY INJECTION<br>(2) | BY MOUTH<br>(3) |
|---------------------|---------------------|-----------------|
| Ethinyl estradiol   | 0.020               | 1.2             |
| $\alpha$ -Estradiol | 0.025               | 1.1             |
| Diethylstilbestrol  | 0.100               | 0.4             |
| Estrone             | 0.100               | 1.0             |
| Estriol             | 1.100               | 3.0             |

It is apparent from data in Figs. 1, 2, and 3 that if a continuous excretory level of estrogen is to be maintained dosage of the hormone must be administered at least daily. It is also apparent, since daily *injections* of any drug are objectionable when another route is just as efficacious, that oral administration (hormone feeding), or possibly inunction, is the most practical means of effectively maintaining an excretory level of estrogen. Thus it would seem that for those individuals who are able to tolerate orally active estrogens, daily or divided daily doses should be most efficient and practical. Cyclical estrogen therapy for the human being, then, should consist of three weeks of daily hormone feeding followed by a week or more without treatment. If the seven to ten days without treatment falls at the time of expected menstruation in those individuals who have a uterus and who are still menstruating, the production of prolonged or irregular bleeding or amenorrhea can be obviated.

Although the estrogen-withdrawal-bleeding interval has been found to be quite constant in patients with primary amenorrhea and natural menopause, this is not the case in women with varying degrees of ovarian function exhibiting normal or abnormal menstrual cycles. The mechanism responsible for the variation in the estrogen-withdrawal-bleeding interval has been described elsewhere as being a theoretically fluctuating uterine threshold and will not be gone into here (Palmer,<sup>23, 24</sup> 1941). At any rate, it has been found in our series of patients being treated for the menopause by hormone feeding that the beginning of a cycle of estrogen therapy should be the second or third day of a phase of bleeding and that the daily dose given be large enough to stop effectively that phase of bleeding within two or three days. If estrogen withdrawal bleeding occurs at all (when the estrogen used is diethylstilbestrol), it will do so at most seven to eight days after cessation of treatment. Our

estrogen recovery data have revealed that excretion of estrogen ceases, regardless of the dosage, in ovarian inactive individuals in that period of time, and by this criterion we may assume that elimination from the body is complete. No estrogen whatsoever was found in their urine seven days after each of the two patients had received 5 mg. a day for a period of seven days. On the basis of estrogen recovery data, it would seem that the shortest interval between cycles of estrogen therapy should be no less than five days. The interval may be as long as desirable, occasionally, to check the patient's need for further treatment. If, however, the withdrawal bleeding that occurs is alarming as to its profuseness or prolongation, further cyclical therapy should be instituted. When a series of cycles of estrogen therapy has been planned, the successive cycles should be started the second or third day of a phase of withdrawal bleeding just as the first cycle of therapy should be instituted on the second or third day of a phase of spontaneous bleeding.

It has frequently been found that the daily dose of estrogen required in cyclical therapy for the menopause is small enough so that the withdrawal intervals are not associated with bleeding or that in individuals in whom withdrawal bleeding has been induced the dose can be lowered and still be effective, so that withdrawal bleeding does not recur. On the other hand, it has also been found that some individuals seem to require a daily dose, for the relief of symptoms, that is always followed by bleeding during the withdrawal intervals. Irradiated patients are the least likely to have withdrawal bleeding even with sizable doses. Hysterectomized women, if hysterectomy has been adequate, of course do not bleed, and it is in these cases where the need for cyclical estrogen therapy may justifiably be questioned. Because of the experimental observations reported above in which uninterrupted treatment has been shown to produce harmful effects and because even the most experienced of us are still in the early phases of investigation of potent estrogen therapy, it would seem advisable that cyclical therapy should be observed in all cases, even though uterine bleeding is not a factor with which we need to contend.

#### THE USE OF ESTROGEN ESTERS

The protracted effect of estrogen esters has been established in the laboratory by many workers (Miescher and others,<sup>31, 32</sup> 1938), and the protracted effect of them in human beings has been observed by most clinicians who have used and compared the effects of esterified and unesterified estrogens. Weight for weight, the dipropionic acid ester of  $\alpha$ -estradiol has been found to be the most protracted in its effect in experimental animals and it seems also to be most enduring in its effect clinically. Heavier estrogen esters by virtue of increased length of the nonestrogenic hydrocarbon radicals have been used in the laboratory

and found to have an even greater protracted effect, the protraction varying directly with the length of the side chains. The dipropionic ester of  $\alpha$ -estradiol, however, is the largest molecule available commercially for clinical use at present.

Accurate estrogen-withdrawal-bleeding data for estrogen esters in human beings are not available at present. It is possible to state, however, from observations on primates (Engle and Crafts,<sup>33</sup> 1938; Zuckerman,<sup>21</sup> 1941) that contrary to the fact that the estrogen-withdrawal-bleeding interval does not vary markedly with the dose of unesterified estrogen used, the interval does vary directly with the dose of estrogen ester used.

The use of estrogen esters is to be preferred in individuals who cannot tolerate hormone feeding. Small doses from 0.1 to 1.0 mg. at intervals probably not less than seven days can be administered, usually without the advent of endometrial stimulation and bleeding. If larger doses are required for the relief of symptoms, intervals of two weeks or longer after a series of three or six weekly injections probably should be observed for the occurrence of withdrawal bleeding in the rhesus monkey. The larger the dose used the longer the withdrawal interval should be. The restarting of a cycle of therapy with an estrogen ester may be made with the onset of a menstrual period or a phase of withdrawal bleeding.

Cyclical therapy by hormone feeding has, in our hands, produced the best immediate results and has been the most economical and practical. Some patients who have been followed have required no more than one cycle of treatment, with the occasional repetition of a second cycle of treatment a few months later. If a second cycle seems indicated immediately, then plans are made to follow a cyclical regime for six months before stopping treatment. This plan may be followed by the failure of recurrence of menopausal symptoms when the six months' regime has ended. However, the problem of how it will all end for those few patients for whom cyclical estrogen therapy seems to be required month after month remains unsolved for the present.

There is some experimental data to support the view that estrogen esters may yet prove the preferable means by which the treatment of the menopausal woman can be carried out most successfully. Markee<sup>34</sup> (1940) has observed that gradually decreasing doses of estrogen make for the prevention of withdrawal bleeding. This is the effect in a general way of estrogen esters as compared with unesterified estrogens (Engle and Crafts,<sup>33</sup> 1938). Where withdrawal bleeding may be a desirable result, as in primary amenorrhea, such bleeding is most efficiently produced by large doses of unesterified estrogens being suddenly withdrawn. The sudden fall in estrogen level produced in this manner is usually followed by uterine bleeding. This effect is not so easily produced with hormone esters having a protracted effect or by the

use of pellets of estrogen. In an experiment on a rhesus monkey where diethylstilbestrol pellets were implanted subcutaneously, complete absorption of the pellets took place and cystic glandular hyperplasia of the endometrium was produced but bleeding did not occur even after a sufficient interval was observed.

#### CLASSIFICATION OF ESTROGENS

Estrogens may be classified in at least three ways: First, according to their relative potencies as determined by a standard laboratory procedure; second, according to their relative potencies by oral vs. parenteral administration; and third, according to their duration of action. Peculiarities in chemical structure, solubility, absorption, fate and excretion of estrogens prohibit any sort of correlation between these three classifications.

Emmens<sup>35</sup> (1938) has determined the data necessary for classification of estrogens according to the first two points. Table I lists the estrogens with which we may be concerned in the order of their potency as determined by a standard procedure. Column 2, Table I, lists the least amount of crystalline hormone in micrograms by injection necessary to produce estrus in 50 per cent of a group of ovariectomized mice. Column 3, Table I, lists the least amount of crystalline hormone in micrograms which by oral administration is necessary to produce estrus in 50 per cent of a group of ovariectomized mice.

The third point in the classification of estrogens is simply one of grouping them either as simple estrogens or estrogen esters and can be appreciated only when administration of them is by injection. All of the estrogens themselves are relatively short lived and have a transient effect while their esters are long lived and protracted in action.

#### SUMMARY AND CONCLUSIONS

The harmful effects of continuous as opposed to cyclical estrogen treatment in experimental animals and human beings have been reviewed and discussed. The release of diethylstilbestrol for general use makes it necessary to observe certain principles of treatment that were relatively unimportant before the advent of inexpensive and highly potent estrogens.

The recommended therapeutic dose of diethylstilbestrol for cyclical therapy in menopausal women varies between 0.1 and 0.5 mg. daily by mouth for twenty-one days, followed by a five- to ten-day interval without therapy. The estrogen withdrawal interval should fall at the time of expected menstruation, and cycles of therapy should be started twenty-four to forty-eight hours after the onset of a new phase of uterine bleeding if it occurs.

The recommended therapeutic dose of diethylstilbestrol for cyclical therapy in young women with hypoovarian amenorrhea or primary

hypogonadism is 1 mg. daily for seven days followed by 5 mg. daily for seven days (total dose 42 mg. in fourteen days). The estrogen withdrawal interval should be fourteen days, so that subsequent cycles of therapy may be started at twenty-eight-day intervals.

Cyclical, as opposed to continuous, estrogen therapy is strongly recommended in all hypoovarian conditions, even though the absence of the uterus precludes the occurrence of bleeding as a troublesome factor.

At least daily, as opposed to less frequent, administration of diethylstilbestrol or other unesterified estrogens during a cycle of therapy is recommended for the purpose of maintaining an excretory and probably a circulating estrogen level.

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# GLOMERULAR FILTRATION AND RENAL BLOOD FLOW IN "NORMAL" PATIENTS FOLLOWING TOXEMIAS OF PREGNANCY

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## INTRODUCTION

THE frequency with which the "toxemias of pregnancy" tend to recur<sup>1, 2</sup> together with the high incidence of hypertensive disease and the vascular and renal pathology<sup>3-5</sup> which obtain in posttoxemic women has formed the basis for many of the etiologic concepts of the disease and has greatly influenced the methods of therapy in the acute phases as well as in the care of the patient post partum.<sup>6</sup>

It is not infrequent, however, to find patients who have had one of the clinical types of the disease but who fail to demonstrate any residual pathology by clinical and laboratory methods and who go through a subsequent pregnancy in a normal manner. The presence of such patients has played a large part in leading many students of the disease to believe that "toxemia of pregnancy" is not a clinical entity but is in reality a syndrome associated with several basic diseases and becoming manifest during a pregnancy.<sup>7</sup> It is believed that the amount of renal and vascular damage found in prolonged follow-up studies<sup>8-10</sup> is proportional to the length and severity of the acute ante-partum stage.

We were unable to demonstrate an increased incidence of hypertension in any age group among women who had had term pregnancies when compared with patients who had never been pregnant.<sup>11</sup> These results were interpreted to mean that the "toxemias of pregnancy" leave no residual hypertension-producing lesion, but that the disease probably occurs in only those patients who have a "hypertensive type" of vascular system.

In routine examination of apparently normal patients by the diodrast clearance, it has been noted in some cases that the renal blood flow is definitely depressed,<sup>12, 13</sup> although a depression of this function is usually associated with hypertension. A definite depression of the renal blood flow has been demonstrated immediately post partum in the "toxemic" patient<sup>13, 14</sup> although it may be normal prior to delivery.<sup>13-15</sup>

Such observations suggest that clinically normal patients may have the same inherent vascular pathology as subjects with outspoken hyper-

tensive disease. It seems likely that one might encounter a greater incidence of nonhypertensive vascular disease as well as of hypertensive vascular disease among posttoxemic women than in the population at large.

The following experiments are designed to determine the incidence of depressed renal blood flow in "posttoxemic" women who are normal to other clinical and laboratory tests.

#### MATERIALS AND METHODS

Six patients who were at term and known to have had a toxemic pregnancy from one to five years previously were studied before the onset of labor and again seven to ten days post partum. Two of the patients had had one normal pregnancy since the one associated with the toxemia, two had had normal pregnancies prior to the abnormal one, and two had had only the previous pregnancy which was associated with hypertension and albuminuria.

Nine patients who had had a pregnancy toxemia from six months to twelve years previously were not pregnant at the time of the study.

All patients were known to have had a hypertension and albuminuria associated with a pregnancy and all but one had had several blood pressure recordings and urine examinations since that time. No patient was included on whom the record of the antenatal course and delivery was not available and on whom the follow-up had shown an elevation of blood pressure of 140 and/or 90 mm. Hg. or more, albuminuria, or evidence of eye ground changes.

At the time these renal function tests were done, each patient was thoroughly studied clinically. Blood pressure readings below 140 systolic and 90 diastolic were considered normal. The urine was found negative to Esbach's solution and microscopic examination of centrifuged sediment showed no abnormal constituents. The eye grounds were carefully examined and found normal. No cardiac enlargement or peripheral vascular thickening was noted.

The technique used for the renal function studies was the same as that described previously,<sup>12</sup> except that the bladder was routinely washed with 30 c.c. of saline which was expelled by 100 c.c. injections of air and that all diodrast determinations were made by Alpert's method.<sup>16</sup>

#### RESULTS

*Patients in Normal Pregnancy Following Toxemic Gestation.*—Five of the 6 patients of this group were studied antepartum, and a summary of the clinical and laboratory findings are given in Table I.

In one patient no satisfactory clearances could be obtained because of low urine flows. The inulin clearance values in the remaining 4 showed normal values for 2 and definite depression of this clearance in the other 2. The mean was found to be depressed to 84 c.c. per minute as compared with 116 c.c. per minute for the normal.<sup>13</sup> The diodrast clearance was definitely depressed in one patient but the remaining 3 of this group showed nearly normal values. The mean for the group (499 c.c. per minute) was definitely below the normal mean of 636 c.c. per minute. As is to be expected, the renal blood flow is likewise minimally depressed and the filtration fraction is found to be approx-

TABLE I  
SUMMARY OF CLINICAL DATA AND CLEARANCE VALUES OF SIX PATIENTS WITH PREVIOUS TOXEMIA OF PREGNANCY DURING A NORMAL PREGNANCY\*

| CASE                                 | AGE | PAR-ITY | WEEKS<br>A.P.<br>DAYS<br>P.P. | BLOOD<br>PRES-<br>SURE<br>MM.<br>HG. | ALB.   | C.V.     | YEARS<br>SINCE<br>TOX-<br>EMIA | INULIN<br>CLEARANCE<br>C.C./MIN. | DIODRAST<br>CLEARANCE<br>C.C./MIN. | RENAL<br>BLOOD FLOW<br>C.C./MIN. | UREA<br>CLEARANCE<br>C.C./MIN. | URIC ACID<br>CLEAR-<br>ANCE<br>C.C./MIN. | FILTRATION<br>FRACTION      | REMARKS  |
|--------------------------------------|-----|---------|-------------------------------|--------------------------------------|--------|----------|--------------------------------|----------------------------------|------------------------------------|----------------------------------|--------------------------------|--|-----------------------------|--|
| 1A                                   | 28  | 2-0-2   | n.d.                          | 120/80                               | 0      | 44       | 5                              | 128 100                          | 480 540 530                        | 840 960 940                      | 119 117 103                    | 47 37 34                                 | 0.26 0.19                   | 1st Preg. 1936, M.P.E.<br>2nd Preg. 1938, normal                           |
| 2A                                   | 38  | 4-2-1   | 40                            | 120/80<br>110/70                     | 0<br>0 | 34<br>32 | 5                              | 61 58 56<br>60 60 61             | 530 650<br>455 392 393             | 800 990<br>680 590 580           | 52 57<br>55 57                 | 30                                       | 0.11 0.09<br>0.13 0.15 0.15 | 1st Preg. 1936, S.P.E.<br>2nd Preg. 1939, normal                           |
| 3A                                   | 33  | 3-0-0   | 40                            | 120/70<br>130/85                     | 0<br>0 | 38<br>43 | 4                              | 102<br>125 121                   | 530<br>412 373                     | 860<br>720 680                   | 90<br>73 71                    | 35<br>43 35 32                           | 0.20<br>0.29 0.31           | 1st Preg. 1935, normal<br>2nd Preg. 1936, normal<br>3rd Preg. 1937, S.P.E. |
| 4A                                   | 25  | 2-0-1   | 38                            | 120/70<br>110/60                     | 0<br>0 | 36<br>38 | 2                              | 77 64 71<br>44 47                | 330 282 345<br>216 275 305         | 515 440 545<br>345 450 490       | 50 58<br>58                    | 11 15 12<br>12 11 12                     | 0.23 0.23 0.21<br>0.2 0.17  | 1st Preg. 1937, normal<br>2nd Preg. 1939, S.P.E.                           |
| 5A                                   | 20  | 1-0-1   | 40                            | 138/85<br>130/70                     | 0<br>0 | 28<br>43 | 1                              | 151 135 143<br>129 139           | 440 315<br>640 690                 | 850 850<br>1000 1050             | 66 76 66<br>55 52              |  | 0.29 0.31<br>0.20 0.20      | 1st Preg. 1940, S.P.E.<br>1st Preg. 1940, M.P.E.                           |
| 6A                                   | 30  | 3-1-0   | 40                            | 130/70                               | 0      | 35       | 1                              | 84.1<br>97.9                     | 499.6<br>394.3                     | 750.0<br>690.4                   | 59.0<br>77.8                   | 17.6<br>29.2                             | 0.1854<br>0.2245            |  |
| Ante-partum mean<br>Post-partum mean |     |         |                               |                                      |        |          |                                |                                  |                                    |                                  |                                |  |                             |  |

\*In this and the following table, Ecl., denotes eclampsia; M.P.E., mild pre-eclampsia; and S.P.E., severe pre-eclampsia; n.d., not done.

imately normal (0.18). The urea clearance seems to be definitely depressed in each instance and the mean is found to be 59.0 c.c. per minute. The uric acid clearance is found to be normal in two instances and definitely depressed in two; the mean is minimally depressed (17.6 c.c. per min.).

Post-partum clearances were run on 5 of the patients and satisfactory clearances obtained. In 2 instances the clearance of inulin was more than moderately decreased and in the remaining 3 the values were normal. The mean was minimally depressed (97.9 c.c. per minute) but tended to return toward normal as compared with the ante-partum value. The diodrast clearance gave normal values in only one instance and in one patient was extremely depressed. The mean tended to deviate from normal following delivery and represents a considerable reduction in this clearance (394 c.c. per minute). The renal blood flow parallels the diodrast depression and is likewise noticeably decreased (690 c.c. per minute). The filtration fraction (0.22) remains about normal although slightly higher than the ante-partum value. The urea clearance rises to 77 c.c. per minute. The uric acid values were obtained on only two patients.

*Posttoxicemic Nonpregnant Patients.*—The values for both the clinical and the laboratory studies are given in Table II.

The inulin clearance seems to be depressed in direct proportion to the time elapsed since the toxemic pregnancy and no normal values are obtained for those who are more than one year post partum. The mean for the group (94 c.c. per minute) is reduced. The diodrast clearance is definitely normal in only 3 patients, only one of whom was more than one year post partum. In two patients the values are severely reduced. The mean (468 c.c. per minute) is definitely low and the blood flow in the kidneys (780 c.c. per minute) parallels this low value. The filtration fraction remains normal (0.20) and the urea clearance is minimally depressed (78 c.c. per minute) but not remarkably so. The uric acid clearance is normal (30 c.c. per minute).

#### DISCUSSION

The patients in this series were examined clinically and by the usual laboratory renal function studies and were considered entirely normal. One group had sustained an additional test, that of the pregnancy, and failed to show evidence of renal or vascular abnormality. In this group both the renal blood flow and the glomerular filtration rate were reduced, similar to values seen previously in pregnant women who were known to be hypertensive before pregnancy and who showed hypertension and albuminuria during the tested pregnancy.<sup>13</sup> It seems reasonable to suppose that all patients who have had toxemia of pregnancy have the same vascular lesion regardless of the blood pressure level.

Some factor associated with pregnancy in these patients, as in those previously reported, apparently has the ability to increase the renal blood flow and to decrease glomerular filtration.

The clinical implications of these findings are of interest and deserve further investigation. If a patient having hypertension following a toxemic pregnancy is advised against a future pregnancy, it would seem

TABLE II. SUMMARY OF CLINICAL DATA AND CLEARANCE VALUES OF NINE PATIENTS WITH PREVIOUS TOXEMIA OF PREGNANCY WHO ARE NOW NORMAL

| CASE | AGE | PARITY | BLOOD PRES-<br>SURE<br>MM. Hg. | YEARS SINCE<br>TOXEMIA<br>TYPE OF<br>TOX. | C.V. | INULIN<br>CLEARANCE<br>C.C./MIN. | DIOBRAST<br>CLEARANCE<br>C.C./MIN. | BLOOD FLOW<br>C.C./MIN.       | UREA<br>CLEARANCE<br>C.C./MIN. | URIC ACID<br>CLEARANCE<br>C.C./MIN. | FILTRATION<br>FRACTION |
|------|-----|--------|--------------------------------|---|------|----------------------------------|------------------------------------|-------------------------------|--------------------------------|-------------------------------------|------------------------|
| 1B   | 32  | 1-0-0  | 130/85                         | 12 years<br>S.P.E.                        | 38   | 52 53                            | 475 440                            | 770 715                       | 85 77                          | 38 32                               | 0.11 0.12              |
| 2B   | 45  | 6-4-2  | 120/74                         | 9 years<br>S.P.E.                         | 40   | 73 80                            | 650 520                            | 1080 870                      | 82 74                          | 35 32                               | 0.18 0.15              |
| 3B   | 40  | 2-0-1  | 130/88                         | 6, 4 years<br>S.P.E.                      | 37   | 95 94 94                         | 425 425 460                        | 680 680 735                   | 60 75 65                       | 21 17 26                            | 0.22 0.22 0.20         |
| 4B   | 26  | 1-0-0  | 120/70                         | 3 years<br>Ecl.                           | 30   | 98 95                            | 325 355                            | 465 510                       |                                |                                     | 0.30 0.27              |
| 5B   | 28  | 1-0-0  | 130/75                         | 1½ years<br>Ecl.                          | 36   | 88 102                           | 445 445                            | 760 760                       | 65 65 67                       | 27 29 25                            | 0.19 0.22              |
| 6B   | 22  | 1-0-1  | 130/85                         | 1 year<br>S.P.E.                          | 40   | 68 78 79<br>113* 129*            | 390 356 325<br>372* 374*           | 650 600 700*                  | 68 76 68                       | 25 26 28                            | 0.17 0.22 0.25         |
| 7B   | 30  | 1-0-1  | 130/85                         | 1½ years<br>S.P.E.                        | 40   | 95 84<br>164* 137*               | 400 450<br>760* 570*               | 666 750<br>1130* 850*         | 81 74 93                       | 37 28                               | 0.23 0.19              |
| 8B   | 23  | 1-0-1  | 120/70                         | 1 year<br>S.P.E.                          | 40   | 125 136<br>120* 128*             | 630 535<br>790* 800* 840*          | 1050 892<br>1250* 1260* 1280* | 85 105                         | 47 53                               | 0.20 0.25              |
| 9B   | 25  | 1-0-1  | 130/75                         | 1 year<br>S.P.E.                          | 40   | 147 150                          | 680 640                            | 1133 1067                     | 96 96 98                       | 25 24                               | 0.22 0.23              |
|      |     |        |                                |   |      | 94.3                             | 468.5                              | 780.6                         | 78.3                           | 30.3                                | 0.207                  |

\*Clearances immediately post partum after the toxemic pregnancy. The values are not included in the mean.

reasonable that a nonhypertensive posttoxemic patient should get the same advice. It would also seem likely that the greatest factor in producing vascular changes in these patients is time, and that further investigation might show that less emphasis could be placed on the interruption of the pregnancy for the mother's future welfare and more effort be made to obtain a viable baby.

The renal physiology associated with the syndrome is of considerable interest. Repeated demonstrations have been made in hypertensive disease that the filtration fraction is increased, i.e., glomerular filtration is not reduced proportionately to the renal blood flow,<sup>17, 18</sup> but most of this work has been done on male subjects. The increase in filtration fraction has been interpreted as being caused by a constriction of the efferent arteriole of the glomerulus without concomitant constriction of the afferent vessel. Lampport<sup>19</sup> has recently devised a formula for calculating the resistance in arterioles of a fixed system with values obtained by the inulin and diodrast clearances. We have applied this formula to our data (Table III) and find that the total arteriolar resistance is minimally increased in our posttoxemic patients as compared to our normal group.<sup>13</sup>

TABLE III. CALCULATED AFFERENT AND EFFERENT ARTERIOLAR RESISTANCE BY POISEUILLE'S LAW SHOWING MINIMAL CHANGES EFFECTED BY ALTERED RENAL BLOOD FLOW AND FILTRATION AS COMPARED TO THAT PRODUCED BY ELEVATION OF SYSTEMIC BLOOD PRESSURE\*

| GROUP                             | FILTRATION FRACTION | RENAL BLOOD FLOW | MEAN BLOOD PRESSURE | P <sub>G</sub> GLOMERULAR PRESSURE | RA AFFERENT AR-TERIOLAR RESISTANCE | RE EFFERENT AR-TERIOLAR RESISTANCE | R TOTAL AR-TERIOLAR RESISTANCE | RA/RE |
|-----------------------------------|---------------------|------------------|---------------------|------------------------------------|------------------------------------|------------------------------------|--------------------------------|-------|
| Normal pregnancy (ante partum)    | 0.18                | 950              | 100                 | 57.22                              | 32.77                              | 20.10                              | 44.07                          | 1.190 |
| Normal pregnancy (post partum)    | 0.22                | 979              | 100                 | 60.74                              | 19.67                              | 22.35                              | 42.02                          | 0.880 |
| Posttoxemic (antepartum)          | 0.19                | 750              | 100                 | 57.91                              | 29.45                              | 25.71                              | 55.16                          | 1.145 |
| Posttoxemic (post partum)         | 0.22                | 690              | 100                 | 59.70                              | 28.99                              | 30.71                              | 59.70                          | 0.944 |
| Posttoxemic (nonpregnant)         | 0.21                | 781              | 100                 | 59.00                              | 26.88                              | 24.54                              | 51.42                          | 1.095 |
| Hypothetical hypertensive, normal | 0.22                | 1000             | 160                 | 60.74                              | 79.26                              | 21.90                              | 101.15                         | 3.619 |

\*  $P_g = P_o' + 20$   
 $RA = \frac{P_m - P_o' - 40}{HD}$   
 $RE = \frac{(1 - kF) (P_o' - P_o + 10)}{HD}$   
 $R = RA + RE$   
 $P_o'$  = Osmotic pressure of unconcentrated blood in mm. Hg.  
 $P_o$  = Osmotic pressure of concentrated blood in glomerulus in mm. Hg.  
 $HD$  = Renal blood flow.  
 $P_m$  = Average of systolic and diastolic brachial artery pressure.

These changes in arteriolar resistance, however, are minimal and certainly of no great significance when compared with resistances computed on a hypothetical case having normal diodrast and inulin clearance values but a moderately elevated mean pressure (Table III). The values for total resistance and afferent arteriolar resistance are markedly increased in such a case, whereas the efferent arteriolar resistance and glomerular pressure are unaltered.

If this formula can be applied in general to a dynamic system such as the vascular bed, it would seem that the fundamental physiologic basis of this disease is reduced vascular flow, specifically through the kidney. Alteration in vascular tone (spasm) ensues only after hypertension develops and merely serves to maintain the low flow.

#### SUMMARY

Renal blood flow and glomerular filtration have been determined on 6 pregnant and 10 nonpregnant women who have had a toxemia of pregnancy from one to twelve years previously and who have been considered normal by both clinical and laboratory methods since.

Reduction of the renal blood flow and glomerular filtration is noted on most patients and is generally correlated with the length of time since the toxemic pregnancy.

The presence of a pregnancy usually is associated with higher values than are noted post partum, but the findings in these patients are not unlike those in the posttoxemic hypertensives who have a recurrent toxemia.

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# THE ROUTINE USE OF BICYCLE EXERCISES FOR THE PROPHYLAXIS OF POSTOPERATIVE THROMBOPHLEBITIS

## A PRELIMINARY REPORT

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THE exact incidence of thrombophlebitis occurring as a postoperative complication is difficult to find in the various papers and monographs that appear on the subject, but Thorek<sup>1</sup> suggests it to be around 1 per cent. He states, though, that in Kümmell's clinic, at Göttingen, some thrombophlebitis was seen in more than 4 per cent of their laparotomies. He further relates that clinics of other men report figures variously from 1 to 5 per cent. Barker and his associates<sup>2</sup> recently report a study of 172,888 operative cases of which 1,665 developed thrombosis with or without embolism or embolism with or without other evidence of thrombosis. Crafoord,<sup>3</sup> in 1,054 patients subjected to operation for gynecological disorders, records an incidence of 4 per cent.

## ETIOLOGY

Any consideration of the possibility of prophylaxis for such a complication should be preceded by a knowledge of the factors which predispose to the condition. We find in a review of the available literature a wealth of information rather carefully worked out on this point.

Barker and others<sup>2</sup> in an analysis of their 1,665 consecutive cases of postoperative venous thrombosis and embolism, found that thrombophlebitis had a greater incidence in women than in men with a ratio of 3:2. The complication was rare before the age of 20 and more than 50 per cent of the cases in men were found in patients between the ages of 50 and 69 years; more than 60 per cent of the cases in women were found in patients between the ages of 40 and 59 years. It is thus seen that this complication develops in women in earlier age groups than in men.

This group studied various disorders of their patients with reference to possible predispositions for this complication and, as a result, believe that patients with the following conditions show a definite, though not marked, tendency to develop thrombophlebitis: (1) Obese patients; (2) patients with blood disease, such as, secondary and hypochromic anemias, polycythemia vera, leucemia, primary anemia, hemolytic icterus, and thrombocytopenic purpura; (3) patients with diseases of the peripheral veins, such as, varicosities or previous thrombophlebitis either recent or



old; (4) patients with cardiac disease, e.g., chronic valvulitis, hypertensive heart disease, coronary heart disease, and auricular fibrillation; (5) severe infections either as an indication for the operation or as a postoperative complication; and (6) carcinoma.

It is interesting to note that while the above may be present singly or in various combinations in some patients, there were about one-third of their patients who developed this complication and showed no evidence of any of these predisposing factors.

The fact that patients exhibiting marked varicosities of the legs are prone to develop postoperative thrombosis in these is well recognized, and hence any factor which would predispose to the development of the former might, in a way, be effective in aiding the production of the latter.

Boyd<sup>3</sup> lists four exciting factors in the production of these varicosities, i.e., (1) central obstruction to the venous return as in mitral stenosis, emphysema, cirrhosis; (2) pressure of a tumor, gravid uterus, or loaded rectum; (3) prolonged standing; and (4) straining and violent muscular efforts.

For an excellent consideration of the entire subject of thrombophlebitis with an adequate nucleus for a bibliography the reader is referred to the article by Homans on thrombosis found in Mason's text.<sup>4</sup> This investigation of the problem considers three local anatomic causes and as many general contributing causes. The first of these include: (1) The veins must be of good size; (2) the vein must have entering branches or large valves or turns or pockets which would present opportunities for eddies and confused currents; and (3) the vein usually is so situated that any of a variety of conditions can slow the current, even for considerable periods. It is readily seen how the upper femoral and iliac veins as well as the venous plexuses of the pelvis and varicosities of the legs conform to the above-mentioned conditions.

The essential points of this entire problem seem, to the author, to be summed up in Homan's discussion of the following which he calls general contributing factors. The first of these are disorders which tend to alter the vascular endothelium, the second are disorders in which the character of the blood is altered and the third are disorders causing sluggish circulation either over the whole body or part of it.

The disorders which tend to alter the vascular endothelium are found in the form of inflammations and degenerations as seen in various septic states, influenza, typhoid fever, and the like, but these are the least important practically since proof of alteration of the endothelium is lacking.

Many factors may influence the character of the blood and not the least among these are states of dehydration brought on by diarrhea, vomiting, hemorrhage, or sweating. All of these are readily recognized as being closely associated both preoperatively and postoperatively in

surgical patients. Other states influence the character of the blood, such as the toxemias, either chemical or other, nephritis, diabetes, the puerperal state, trauma of accidents and surgical procedures.

It is the third group of disorders which cause sluggish circulation that particularly concern this paper. In this class are found the immobility that so frequently follows operations or prolonged illnesses, increased intra-abdominal pressure caused by reclining or sitting up in bed, vomiting, coughing, distention, and tight abdominal binders as well as the congestion of pelvic veins as in pregnancy.

Smith and Allen,<sup>5</sup> by their studies on the rate of venous flow, noted the time required for the blood to flow from the foot to the carotid sinus in both normal individuals and in patients convalescing from operations. They concluded that there was a definite decrease in foot-to-carotid circulation time within a few hours postoperatively. Two days afterward the time was greater than preoperatively. Beginning with the fifth day postoperative, the average time increased gradually to a value which at the tenth day was approximately 50 per cent greater than the preoperative average. It was their opinion that slowed venous circulation is not the sole cause of postoperative thrombosis, but it is a very important one.

#### PROPHYLACTIC PROCEDURES

In the prevention of thrombosis and embolism, Homans attacks the problem from three different approaches. The first of these are measures to keep the fluid level normal and here the proper administration of fluids by the subcutaneous and/or intravenous routes is to be remembered. The control of vomiting, diarrhea, and hemorrhage are all items to be considered, not just for their immediate effects but for the possibility of their causing a complication at some future date as well. An important source of fluid loss, which is so frequently overlooked in our overzealous endeavor to prevent chilling of the patient postoperatively, is the sweating a patient is subjected to by the use of heavy woolen blankets on the operative day and even thereafter. It should be remembered that the temperature of the room would be better controlled and the avoidance of drafts more important than wrapping the operated patient in many blankets.

In an effort to control a rise in the intra-abdominal pressure after the operation, Homans states that one should avoid peritoneal trauma and contamination during the operation, and overloading the stomach with fluids afterward in attempting to adjust the fluid balance. The judicious use of the rectal tube early, and enemas later, will do much to relieve the accumulation of gas in the intestinal tract. Heavy dressings, and tight abdominal binders in particular, are to be avoided. The efficacy of the abdominal binder is doubted even by many men who, through years of habit, continue to use it. A point that is not generally considered is the fact that the sitting or reclining position not only in-

creases intra-abdominal pressure, but also necessitates the blood of the legs to climb to a higher level.

#### EXERCISE IN PROPHYLAXIS

The use of exercise in the prevention of this complication is not a new idea. As early as 1913, Pool<sup>6</sup> suggested the routine employment of systematic exercises in postoperative treatment. His exercises included flexions, extensions, rotations, pronations, supinations and the like, to be carried out at a certain portion of each day under the supervision of nurses. Following their use in a considerable number of patients, he was able to conclude that the general circulation was improved, the

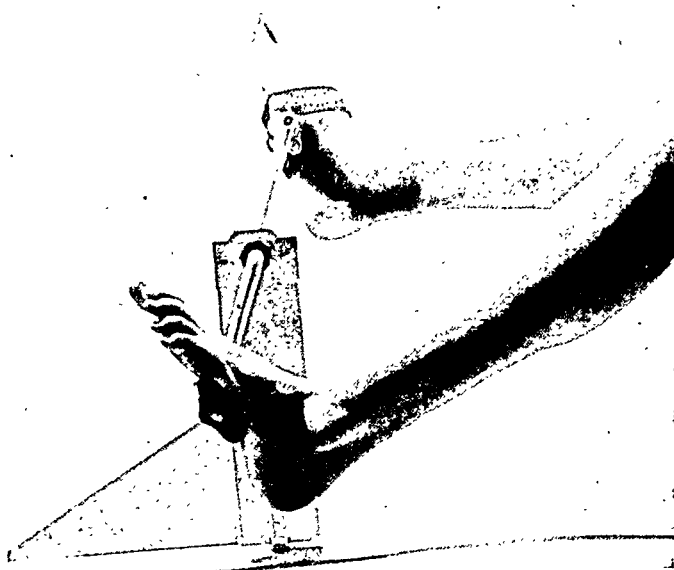


Fig. 1.

functions of the body were performed in more normal manner, the patients felt better, muscular weakness and atrophy were diminished, after getting up exertion was less fatiguing, and return to normal was more rapid.

Smith and his associates<sup>7</sup> found that rapid movement of the legs while in the supine position invariably increased the speed of the blood flow. Elevation to an angle of 30 degrees of the extremities of supine subjects invariably decreased the circulation time. This work, reported in 1941, tends to substantiate the results of Pool and other advocates of the value of exercises and elevation, in the prophylaxis of thrombosis.

Dr. A. P. Martini, formerly associated with the department of gynecology and obstetrics of St. Louis University, at the suggestion of the director of the department, Dr. W. H. Vogt, constructed an apparatus as described by Gamble.<sup>8</sup> This machine is designed with the idea of em-

ploying routine exercises of the lower extremities in a manner that would require a minimum of supervision by the nursing staff and of preparation of the patient.

### RESULTS

The regime instituted by Dr. Martini was to start the exercises on the first day after the operation. On that day, the exercises were taken twice, for five minutes each time. The patients were instructed, by the nurse in attendance, as to how to fit themselves to the apparatus, and shown about the desired speed of motion. On subsequent days, the exercises were increased to ten minutes twice each day and were continued until the patient was out of bed. Usually no care was needed for the patients during the time of these subsequent exercises and thus the nurses were free to attend to other duties.

To offset the lack of exercises on the day of operation, they had the foot of the bed elevated for the first twenty-four hours, either in the Trendelenburg position, or by simple elevation of the lower portion of the springs of the bed. This aids in speeding the venous return flow from the legs as shown by Smith and his co-workers above.

The procedure is a very simple one and is readily adaptable to routine orders on cases such as are encountered on gynecologic wards. The patients themselves are very fond of the exercises. While many of them find it somewhat difficult at first, the greater majority of the patients become very cognizant of the feeling of well-being it gives them. Some of them have requested information regarding the possible purchase of these machines for continued use at home.

The first machine is a homemade outfit, consisting of a base of wood planking. To this is attached a simple upright, likewise of wood, to the top of which are attached the bicycle pedals. When this machine was in operation for only a few weeks, we were fortunate enough to have a patient using it whose husband operated a bicycle rental business, and he made us another one with somewhat more mechanical ability.

Recently we have used the machine for the treatment of a subsiding case of thrombophlebitis before allowing the patient to sit up or get out of bed in an effort to gain back some of the lost tonus caused by the enforced period of rest and elevation for some twelve days.

Interest was instigated in the writing of this paper when, within a period of three days, two postoperative patients developed signs and symptoms of thrombophlebitis. These made themselves manifest on Oct. 10, 1941, and Nov. 2, 1941, respectively. It was around this period when a new supervisor had taken charge of the floor, and she was not thoroughly familiar with our routine. While making rounds we happened to mention to her that these were the first cases of thrombophlebitis that we knew of since the use of the bicycle exercises had been

started. Much to our surprise the sister in charge reported that neither of these patient had had the exercises. It seemed then that it would be worth while to investigate the actual number of patients subjected to this prophylactic regime and to determine the value of this form of treatment.

In going through the records of the patients admitted to the gynecologic service from July 1, 1940, to those discharged by Dec. 31, 1941, we found 705 admissions. Of these, 517 were operated cases; 376 being considered as major operations and 141 as minor operations. Such procedures as dilatation and curettage, cervical biopsies, excisions of Bartholin's cysts, fulguration of fistulous tracts, insertion of stem pessaries, cautery of the cervix and dilatation of the cervix were considered as minors. All laparotomies, colporrhaphies, trachelorrhaphies, radium implants, and colpotomies were considered as major procedures.

The earliest recorded use of the bicycle exercises was on Aug. 7, 1940, and since these were established, 209 patients had these exercises for varying periods of time from three to thirteen days; of these, 198 had major operations and 11 had minor procedures. During this same period of time, there were 308 patients subjected to various gynecologic operations who did not subsequently have the advantage of the bicycle exercises; of these, 178 had major operations and 130 had minor procedures. Of the total 517 operated cases, 6 gave rise to signs and symptoms necessitating the diagnosis of thrombophlebitis. These cases may be given briefly as follows:

CASE 1.—(40-7813.) A 54-year-old housewife was operated upon on Oct. 16, 1940, for a leucoplakia and kraurosis. A radical vulvectomy was done and bicycle exercises were specifically ordered not given as it was feared they might interfere with proper healing of the operative wound. On Nov. 1, 1940, the patient developed a pain in the right groin with a moderate temperature elevation followed later by edema of that lower extremity. She responded to treatment in the form of elevation and ice bags and was discharged on Nov. 12, 1940.

CASE 2.—(40-7881.) A 35-year-old housewife had a vaginal hysterectomy with an anterior and posterior colporrhaphy on Oct. 19, 1940, for procidentia with cystocele and rectocele. The patient ran a septic postoperative temperature course with peaks as high as  $104.5^{\circ}$  for seven days. She had bicycle exercises for the first six days when she developed a secondary hemorrhage which required packing the vagina, and the bicycle exercises were discontinued. On the tenth postoperative day she developed a typical picture of thrombophlebitis in the femoral veins of the left leg. Ice bags and elevation caused gradual return to normal in twelve days. The patient was discharged improved on Nov. 11, 1940, and when last seen in the clinic on Feb. 3, 1941, she had a persistent edema of the left leg.

CASE 3.—(41-5297.) A 46-year-old housewife had a large ovarian cyst arising from the left side removed on July 28, 1941. She was on

TABLE I. SULFANILAMIDE POWDER SUBCUTANEOUSLY

| RABBIT<br>NUMBER | DAYS LATER<br>REOPERATED | FLUID AND<br>NECROSIS SUB-<br>CUTANEOUSLY | MUSCLE LAYER<br>SEPARATION | WOUND<br>DEHISCENCE |
|------------------|--------------------------|---|----------------------------|---------------------|
| 11               | 2                        | +   |                            |                     |
| 12               | 2                        | +   |                            |                     |
| 13               | 4                        |   | +                          |                     |
| 16               | 5                        | +   |                            |                     |
| 17               | 6                        | +   |                            |                     |
| 18               | 7                        |   | +                          |                     |
| 20               | 7                        | +   |                            |                     |
| 28               | 14                       | +   |                            |                     |
| 29               | 14                       |   |                            | +                   |

three, and four days, respectively. At that time all trace of the powder was gone, there was no free fluid, necrosis, or adhesions. There was no evidence of foreign body reaction either grossly or microscopically.

3. To investigate further the peritoneal response, we constructed artificial pouches in various parts of the abdominal and pelvic cavity. Sulfanilamide powder was placed in these pouches and sutured over. An equal number of controls were made with the same 00 plain catgut and no sulfanilamide. These rabbits were operated upon from two to seven days later and biopsies taken. Histologic study failed to reveal any difference between the peritoneum in contact with the powder and where the plain pouch had been made. Five rabbits were used in this series.

TABLE II. CONTROL INTESTINAL SERIES

| RABBIT<br>NUMBER | NO<br>SULFANILAMIDE<br>POWDER | MULTIPLE<br>ADHESIONS | NO<br>ADHESIONS | DIED FROM BLOOD<br>LOSS AND PERITO-<br>NEAL ADHESIONS<br>PRESENT |
|------------------|-------------------------------|-----------------------|-----------------|--|
| 50               | +                             | +                     |                 |  |
| 51               | +                             | +                     |                 |  |
| 53               | +                             | +                     |                 |  |
| 33               | +                             | +                     |                 |  |
| 31               | +                             |                       | +               |  |
| 52               | +                             |                       |                 | +  |
| 30               | +                             |                       |                 | +  |
| 35               | +                             |                       |                 | +  |

TABLE III. SULFANILAMIDE POWDER INTESTINAL SERIES

| RABBIT<br>NUMBER | SULFANILAMIDE<br>POWDER | NO BLOOD<br>NO ADHESIONS | MULTIPLE<br>ADHESIONS | DIED FROM<br>UNKNOWN CAUSE |
|------------------|-------------------------|--------------------------|-----------------------|----------------------------|
| 25               | +                       | +                        |                       |                            |
| 26               | +                       | +                        |                       |                            |
| 28               | +                       | +                        |                       |                            |
| 32               | +                       | +                        |                       |                            |
| 57               | +                       | +                        |                       |                            |
| 60               | +                       | +                        |                       |                            |
| 34               | +                       |                          |                       |                            |
| 54               | +                       |                          | +                     |                            |
| 55               | +                       |                          | +                     |                            |
| 57               | +                       |                          | +                     |                            |
| 58               | +                       |                          | +                     |                            |
| 59               | +                       |                          | +                     |                            |

7 days  
1 day

4. In continuing our work we turned to the fatty tissue as encountered around the bladder, uterine mesentery, and kidney. In 10 rabbits we made an opening in the fat and introduced 0.5 Gm. of sulfanilamide powder. The pouches in the fat were closed over. An equal number

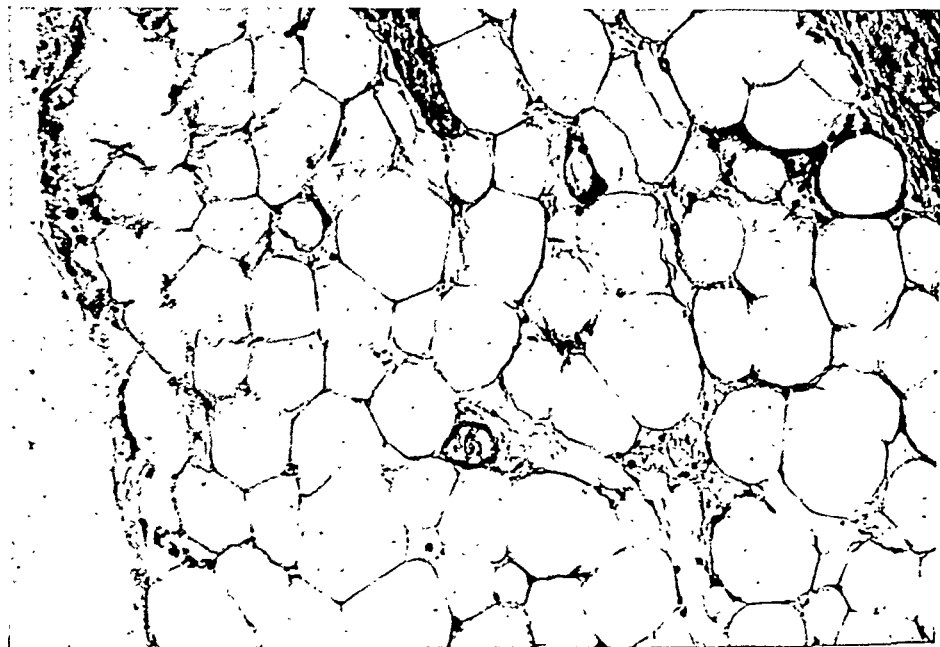


Fig. 1.—Control. Perirenal fat with trauma from a pouch formation and no sulfanilamide powder. Demonstrates mild inflammatory reaction and some regeneration of fat cells. Ten days postoperative.



Fig. 2.—Pouch in perirenal fat with sulfanilamide powder introduced. Demonstrates fat necrosis with inflammation, exudate, and no evidence of regenerating fat cells, ten days postoperative.

of control pouches were made. We found that it took seven days for the powder to be absorbed here. The reaction encountered was striking in that where sulfanilamide was buried in the fat, a marked necrosis took place. Large amounts of serosanguineous fluid was found in the

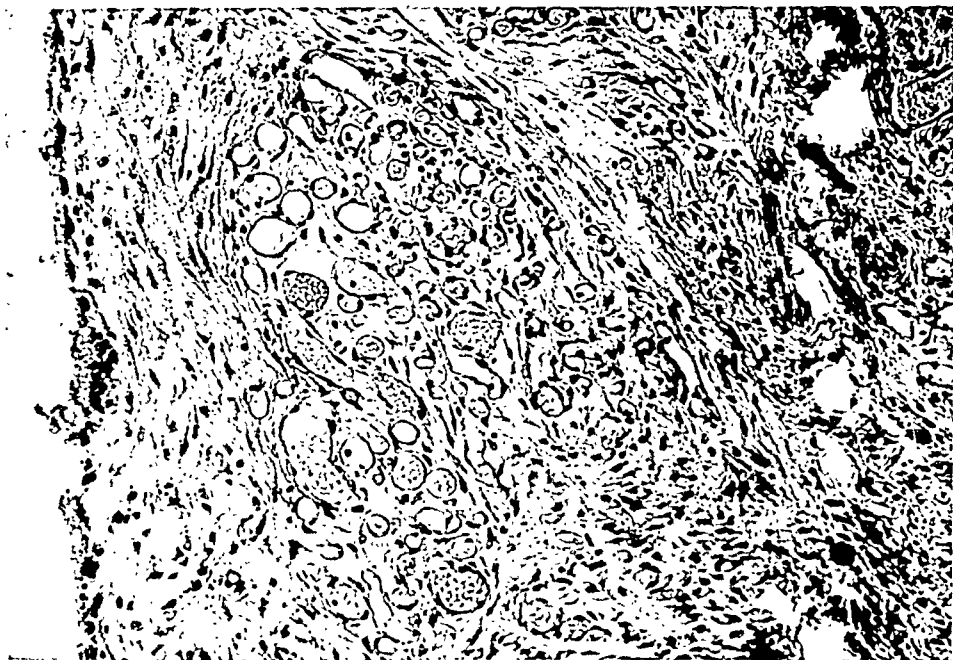


Fig. 3.—Control. Peritoneal pouch. Demonstrates dilatation of capillaries and very mild inflammation. Two days postoperative.

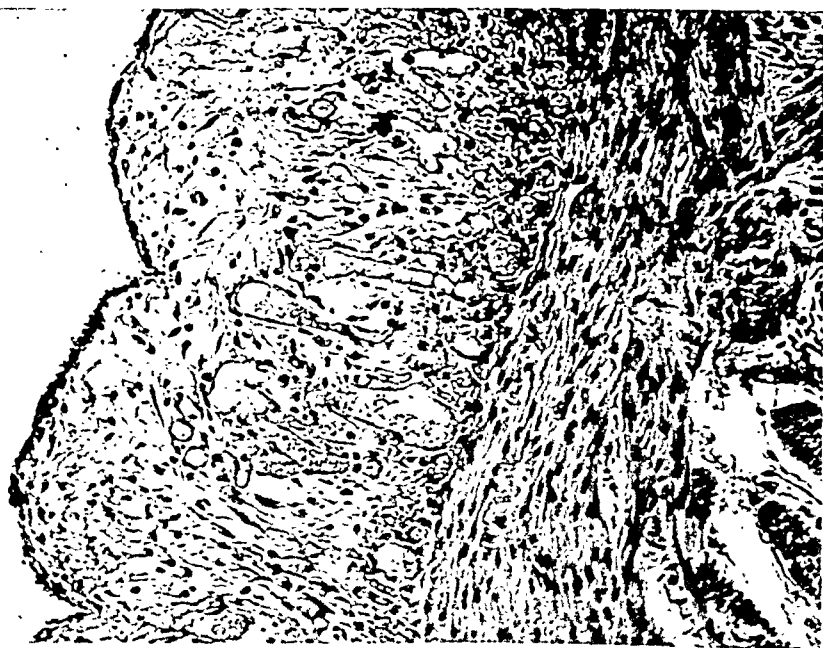


Fig. 4.—Peritoneal pouch with sulfanilamide powder. Histology much like control in Fig. 3. Two days postoperative.



abdominal cavity and a marked generalized peritoneal reaction noted. All ten of the group demonstrated this reaction.

5. In the peritoneal cavity we observed frequent injuries to the small intestinal walls with resultant capillary oozing. Areas thus traumatized would stop bleeding when sulfanilamide powder came in contact with them. Thus it was that we investigated further the possible styptic action of this material by taking long strips (approximately 80 cm.) of serosa off the intestinal walls and sprinkling powder over the raw oozing surfaces. Of 8 control animals, 3 died of blood loss and peritonitis, while none in a group of 12 where sulfanilamide was used died of this cause (Tables II and III). All but one rabbit in the control group developed multiple adhesions while 50 per cent demonstrated this in the sulfanilamide series.

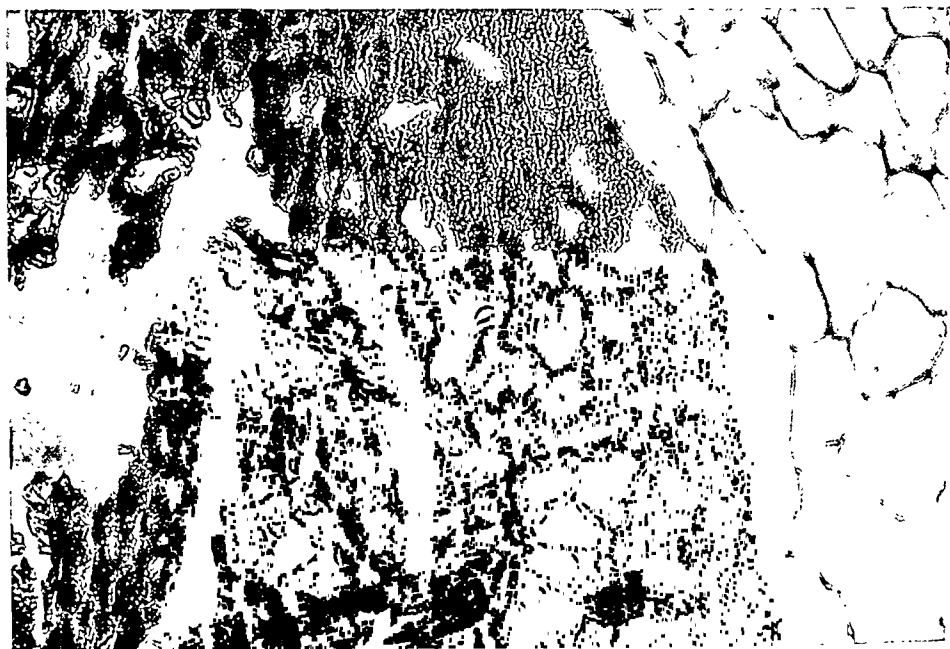


Fig. 5.—Undissolved sulfanilamide powder, showing exudate and crystals in perirenal fat. Six days postoperative.

#### DISCUSSION

We feel that there are several points brought out here which are of clinical significance. Certainly fatty tissue does not tolerate sulfanilamide as it causes necrosis. This is in keeping with a recent statement made to us by R. C. McElroy of the Philadelphia General Hospital, "That where sulfanilamide is used in the incision and closed without drainage, 80 per cent of the wounds break down." T. L. Montgomery using sulfanilamide in the retrovesical space at low cesarean section noted a clinical picture similar to what we obtained in corresponding areas in the rabbit; i.e., fat necrosis with marked peritoneal irritation.

Sulfanilamide in the peritoneal cavity causes no reaction and is readily absorbed. This we have found true clinically.

There seems to be a local styptic action to the powder when applied to an oozing capillary bed. This observation we have found true in pelvic inflammatory disease and endometriosis.

From our studies on the rabbit, sulfanilamide did reduce the incidence of adhesions 50 per cent.

#### CONCLUSIONS

1. Sulfanilamide is safe for use in the peritoneal cavity and is absorbed quickly.
2. Sulfanilamide when used in fatty tissue causes necrosis and typical foreign body response.
3. There is a local styptic action on capillary oozing by sulfanilamide powder.
4. Experimentally there is a reduction in the incidence of adhesions.

5123 WAYNE AVENUE

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#### MACROCYTIC HYPERCHROMIC ANEMIA OF PREGNANCY\*

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**M**ACROCYTIC hyperchromic anemia induced by pregnancy is a rare disease which is believed to be the result of a deficiency of the erythrocyte maturing factor. When it occurs it may present symptoms of the utmost gravity. It is infrequent in temperate climates, but is prevalent in India, where dietary deficiencies are common. The clinical picture begins insidiously with lassitude, dyspnea, palpitation, and pallor which manifest themselves during the last trimester of pregnancy. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea are frequently present. Temperature occurs in about 80 per cent of the cases. Severe symptoms may appear very suddenly, the patient going into collapse and becoming moribund. This may occur just preceding, during, or after delivery. Frequently the symptoms may be mistaken for internal hemorrhage. Retinal hemorrhages are common.

Macrocytic hyperchromic anemia may recur in subsequent pregnancies and be more severe. The maternal mortality in untreated cases is often as high as 90 per cent. If the disease is recognized and proper treatment instituted, the prognosis for both mother and child is good.

This is the first recognized and treated case of macrocytic hyperchromic anemia induced by pregnancy in approximately 18,000 deliveries at the Morrisania City Hospital.

Mrs. M. C., a 29-year-old white, Irish born housewife, para iii, gravida vi at term with no prenatal care, was admitted to the obstetric service of the Morrisania City Hospital on Sept. 8, 1941.

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\*Presented at a meeting of the Obstetrical Section of the New York Academy of Medicine, November 25, 1941.

Her chief complaints were increasingly evident pallor, failing strength, and breathlessness on exertion.

One week before admission she was suddenly seized with sharp, intermittent lower abdominal pains unassociated with either bleeding or vomiting. An ambulance was summoned. The interne prescribed a sedative for what he diagnosed as a gastrointestinal upset, advised her to remain in bed, and referred her to the prenatal clinic. The severity of the pains diminished in character and degree, and finally subsided two days later. Although she remained in bed for the rest of the week, she became aware of an increasing pallor and found herself so weak that she could barely lift her head from the pillow. Becoming greatly alarmed at her progressively failing strength, she recalled the ambulance and was admitted to the hospital.

A review of her past obstetric history revealed two normal full-term pregnancies (1932 and 1933); two abortions induced by emmenagogues (1935 and 1936); and another full-term pregnancy in 1939. Her second pregnancy was associated with mild hypertension and ankle edema. Her past medical and surgical history was irrelevant.

On examination the patient answered questions coherently; she was comfortable, but her appearance was waxy; she resembled one who had sustained the loss of a large amount of blood; her lips and conjunctival mucous membranes were white, her eyes were glassy and sunk deeply in their sockets; the skin was moist but not cold, and there was a fetid odor to her breath. The pulse was rapid, 120, regular and of good quality; respiration 22; blood pressure 130/80; oral temperature 98.6° F. Two small retinal hemorrhages were discernible close to the outer border of the left disc. There was no evidence of glossitis. The heart sounds were of good quality and the lungs were clear. The abdomen was soft and not tender. A small ecchymotic area was seen in the hypogastrium. The liver and spleen were not palpable. The uterus was enlarged to the size of a full-term gestation, was soft, and presented no point of tenderness. The fetal parts were easily palpable and disappeared during a Braxton Hicks contraction. The vertex presented in the left occipitoanterior position and was unengaged. The fetal heart sounds were good. Rectal examination revealed an uneffaced soft cervix. There was no evidence of external bleeding. Slight pitting pretibial edema was present. The knee jerk and ankle jerk reflexes were normal.

Laboratory data on admission revealed: Hg, 18 per cent; red blood count, 850,000; white blood count, 5,500; hematocrit, 12 per cent; total serum protein, 4.9 (Kagan). A catheterized specimen of urine was clear yellow; specific gravity was 1.016, and contained 4-plus albumin and numerous coarsely and finely granular casts. Tests for sugar and acetone were negative.

Obstetric emergencies such as ablatio placentae, placenta previa, or ruptured uterus were considered and excluded by the quality of the pulse, the normal blood pressure, the absence of any abdominal signs or external bleeding, the softness of the uterus and the viability of the fetus.

The most pressing need for the patient at the moment was the immediate administration of blood. Fourteen hundred cubic centimeters of citrated blood were given within a period of fourteen hours. One hour before completion of the transfusion, blood specimens were taken by Dr. B. S. Kahn, hematologist. His report follows: "Hg, 33 per cent

(5.2 gr.); red blood count, 2,100,000; white blood count, 4,200; hematocrit, 18 per cent; reticulocytes, 0.2 per cent; color index, 0.8; volume index, 0.99; neutrophilic polymorphonuclears, 58 per cent; lymphocytes, 40 per cent; monocytes, 2 per cent. The red cells show many oval macrocytes, moderate anisocytosis and poikilocytosis, occasional polychromasia. It must be noted that the indices are not a reliable index of the type of anemia, as the blood examined was withdrawn during transfusion after 1,300 c.c. had entered her circulation. The smear is characteristic of that found in hyperchromic macrocytic anemia. The number of oval macrocytes, the degree of poikilocytosis, and the presence of many hyperlobed polymorphs are significant of an erythrocyte maturing factor deficiency."

At the termination of the transfusion her condition was greatly improved; temperature, 99.4° F.; pulse, 90; and respiration, 20. The blood pressure rose to 140/100, and the patient developed a moderate edema of the face and ankles. Fifty cubic centimeters of a 50 per cent glucose solution were given intravenously to promote diuresis.

The patient was questioned further to determine the etiologic factors responsible for the marked anemia. It was then elicited that she had had severe nausea associated with occasional vomiting, beginning in the second month of gestation. Her distress was only alleviated by abstaining from her usual diet and partaking of small quantities of cereal, vegetables, and milk. During the last two months she subsisted entirely on two glasses of milk and water daily. The total weight gain during her entire pregnancy was three pounds. From the onset of her pregnancy she observed ever increasing lassitude, weakness, and dyspnea in the performance of her daily household duties. At no time had there been any hematemesis, melena, or hemorrhages from any other orifices; nor did the patient complain of headache, sweats, or chills. No drugs had been taken.

From the facts thus far established, a diagnosis of a severe grade of macrocytic anemia was made. It was necessary to determine whether or not the anemia was of the pernicious type. Accordingly, a gastric analysis and a sternal tap were performed. The gastric analysis revealed normal amounts of combined and free hydrochloric acid curves. The sternal puncture was reported by Dr. B. S. Kahn as follows: "Myelocytes, 11.4 per cent; immature polymorphonuclears, 48.6 per cent; mature polymorphonuclears, 9.2 per cent; megaloblasts, 12.4 per cent; erythroblasts, 5.8 per cent; normoblasts, 12.6 per cent. Myelogram is typical of that seen in erythrocyte maturing factor deficiency anemia. It confirms the diagnosis of macrocytic anemia of pregnancy." It could now be definitely stated that the anemia was of dietary origin.

On Sept. 9, 1941, twenty-four hours after admission, the patient was placed on a high caloric vitamin B diet and given 15 units of parenteral liver extract daily. Under this treatment she showed steady improvement. She gained in strength, became more alert, color appeared in her cheeks and lips, her appetite increased, and the edema disappeared.

Additional laboratory studies within the next few days were as follows:

Urine: sp. gr. 1.016, trace of albumin, few granular and hyaline casts

Urine concentration was poor, sp. gr. 1.008, 1.012, 1.010

Blood urea clearance: 22.8 ml. of blood cleared in one minute, 41.3 per cent of normal

Wassermann: negative

Blood chemistry: blood sugar 85 mg. per 100 c.c.  
urea nitrogen 12 mg. per 100 c.c.  
uric acid 7.2 mg. per 100 c.c.

Stool examination: negative for blood and *Dibothyrocephalus latum*

Blood count: (9/12/41) Hg 45 per cent, red blood count 2.2 million, white blood count 9,400

Reticulocyte count showed an excellent response to the specific therapy:

|         |       |
|---------|-------|
| 9/11/41 | 0.1%  |
| 9/12/41 | 0.1%  |
| 9/13/41 | 1.0%  |
| 9/15/41 | 9.0%  |
| 9/16/41 | 25.0% |

On September 17, nine days after admission, at 5:30 A.M., she was abruptly awakened by a severe chill lasting fifteen minutes, associated with headache, malaise, vomiting, marked pain in the right loin, and a temperature of 104° F. Within the next twelve hours she had two more severe chills and with the last, her temperature rose to 107.6° F. There was exquisite tenderness in the right costovertebral angle. A catheterized specimen of the urine showed acid reaction, sp. gr. 1.014, negative for sugar and acetone, 1+ albumin, with moderate number of white blood cells and occasional red blood cells. A blood culture taken at the height of this chill was later reported negative. A diagnosis was made of acute pyelonephritis complicating pregnancy.

Because of this acute episode, a Watson induction was started the following morning. Two milligrams of vitamin K were given as a prophylaxis for hemorrhage. Labor began after 3 minims of pituitrin. After four and one-half hours of strong active pains, a four-pound fourteen-ounce, normal-living male child was born spontaneously. The placenta and membranes were expressed intact. The uterus remained firm. The total blood loss was approximately 100 c.c.

Immediately after delivery the temperature of the mother was 101.6° F., pulse 122, respiration 26, blood pressure 140/90. A blood count taken one-half hour post partum indicated Hg 52 per cent (8 Gm.); red blood count, 2.4 million; white blood count, 10,200; hematocrit, 25 (Wintrobe); color index, 1.1; and volume index, 1.14.

For the first five post-partum days, her temperature fluctuated between 101° and 103° F. She was fairly comfortable and had no complaints. Albumin and a moderate number of pus cells could still be found in the urine. Hexamine and sodium acid phosphate were resorted to for urinary antisepsis. The sulfonamide drugs were not used for fear of depressing hematopoiesis. With the persistence of the temperature and recurrence of chills, the hexamine was discontinued and sulfathiazole substituted. At about the same time ureteral catheterization and retrograde pyelography were done. There was no apparent obstruction in either ureter. Indigo carmine appeared from both ureteral orifices in five minutes. The urine from the right kidney revealed 40 pus cells per high power field. The left side was normal. Cultures from both sides were positive for *B. coli*.

The report of the retrograde pyelogram read: "A moderate dilatation and distention of the right kidney pelvis in the upper half of the right ureter. There appeared to be a fixed point of narrowing in the upper third of the right ureter, which may have represented the crossing of a vessel at this point. The left kidney pelvis, calyces, and ureter appeared to be normal."

Within twenty-four hours after the cystoscopy and use of sulfathiazole, the temperature dropped to 97° F. and remained normal. Sulfathiazole had no effect on the blood picture and was discontinued after five days because of the normal temperature.

The patient's appetite improved, she gained in strength and was completely relieved of all her symptoms. She was allowed out of bed on the seventeenth post-partum day and discharged three days later, at which time her blood count showed: Hg, 9.7 Gm. (62 per cent); red blood cells, 3.1 million; hematocrit, 35 per cent; color index, 1.0; volume index, 1.2. The smear still showed moderate macrocytosis. Anisocytosis less marked. Very few poikilocytes present.

A blood count of the baby taken on the first neonatal day revealed hemoglobin, 22 Gm.; red blood count, 5.4 million; white blood count 14,000. "The smear shows normal red blood cells. No abnormal white cells seen." The baby weighed 6 pounds at the time of the mother's discharge. This was a net gain of 1 pound 2 ounces in three weeks.

#### DISCUSSION

Macrocytic hyperchromic anemia is produced by a deficiency of the erythrocyte maturing factor that is usually formed in the stomach. This hematopoietic principle results from an interaction between an intrinsic factor present in the stomach and an extrinsic factor present in the protein of the diet.

Two facts prove that the above case was one of a nutritional deficiency anemia, namely, the deficient diet, and the reticulocyte response to the specific liver therapy. On admission it was postulated by the medical consultant that the clinical picture was the result of a pre-existent chronic nephritis, in view of the history of hypertension and edema in a previous pregnancy, and albuminuria and casts in the current pregnancy. However, it is well known that renal decompensation will result from the poor nutrition of the kidney cells by the markedly anemic blood, where the hemoglobin content is 30 per cent or less. The function of the kidney tubules depends on a high oxygen concentration in the blood, and where there is a deficiency, as in severe anemia, degenerative changes in the renal epithelium result with the appearance of albuminuria and casts.

Macrocytic anemia of pregnancy is hematologically identical with Addisonian anemia, but unlike the latter, almost always shows free hydrochloric acid in the gastric secretion and will often clear up spontaneously after delivery.

In mild cases of macrocytic hyperchromic anemia, specific liver therapy and a high vitamin B diet are sufficient, but in the more severe cases a blood transfusion is indicated because of the exigencies of labor.

#### SUMMARY

1. A case of a severe grade of macrocytic hyperchromic anemia induced by pregnancy is presented.

2. It was recognized and successfully treated with blood transfusion and parenteral liver therapy.
3. A living male child was delivered spontaneously.
4. A blood count of the child revealed no abnormalities.

We are indebted to Dr. Harry Aranow, Director of Obstetrics, for the privilege of reporting this case.

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## USE OF MERCUROCHROME TO AVOID POSTOPERATIVE CATHETERIZATIONS

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THE prevention or reduction of postoperative catheterizations in a large, active gynecologic service has always been a problem of considerable importance. This is especially true in a charity hospital where prolongation of stay due to bladder or kidney infections, results in a greater cost and a decided decrease in the turnover of patients.

On the Tulane gynecologic service at the New Orleans Charity Hospital, this problem has persisted and we have attempted to combat it by the usual means, such as retention catheters, or routine catheterization after voiding until the residual urine is less than one ounce. The use of urinary antiseptics preoperatively has also been tried. None of these measures have resulted in any material decrease in the number of postoperative bladder and kidney infections.

In the early part of 1940, I began the use of mercurochrome instillation into the urinary bladder as described by Woodruff and Te Linde. The technique was as follows: Instillation of one ounce of 0.5 per cent aqueous solution of mercurochrome into the urinary bladder as soon as the operative procedure is completed and before the patient is removed from the operating room.

A total of 114 patients, upon whom various gynecologic operative procedures had been carried out, were managed in this manner, and, as is shown in Table I, 93 (81 per cent) did not require catheterization.

There were 23 (19 per cent) who did require catheterization, and of this number, there were 11 who were catheterized only once, following instillation of mercurochrome. Many of the patients had a desire to void shortly after reacting from the anesthetic, and quite a few did void at this time. Very few of these required catheterizations at a later time. Inhalation anesthesia was used in all but one case.

TABLE I. RESULTS IN TREATED CASES

|                           |          |
|---------------------------|----------|
| Total number of cases     | 114      |
| Total number of voiding   | 93 (81%) |
| Total number catheterized | 23 (19%) |

In a control series of 97 patients handled by the author at the same hospital, there were 45 (47 per cent) who voided normally, while 52 (53 per cent) required catheterization. The routine postoperative care in this series was catheterization every eight to ten hours when necessary (Table II). These results compare well with those reported by Woodruff and Te Linde and are, as they stated, higher from the standpoint of number requiring catheterization than in many other series that have been reported in the literature.

TABLE II. RESULTS IN UNTREATED CASES

|                           |          |
|---------------------------|----------|
| Total number of cases     | 97       |
| Total number of voiding   | 45 (47%) |
| Total number catheterized | 52 (53%) |

In general, it is well established that catheterization is more frequently necessary when extensive operative work is done about the region of the urinary bladder. With that in mind we have grouped them according to the operation performed, so as to determine the value of mercurochrome instillation in those having surgery about the bladder.

Among the treated patients, there were 28 on whom a laparotomy only had been performed, and of these there were 23 (82 per cent) that voided normally; 5 required catheterization. Of the 12 total hysterectomies in this series, only 3 had to be catheterized. The various operative procedures are shown in Table III.

TABLE III. OPERATIONS IN TREATED LAPAROTOMIES

|  |          |
|--|----------|
| Total abdominal hysterectomy           | 12 cases |
| Supravaginal hysterectomy              | 1 case   |
| Uterine suspensions and appendectomies | 15 cases |

In the control series there were 30 laparotomies; 22 (73 per cent) voided normally, while the remaining 8 were catheterized one or more times. Table IV shows the type of operation in these cases.

The amount of urine voided and the time interval between operation and voiding is of considerable interest. In the 23 treated patients who



TABLE IV. OPERATIONS IN UNTREATED LAPAROTOMIES

|  |          |
|--|----------|
| Total abdominal hysterectomy           | 12 cases |
| Supravaginal hysterectomy              | 4 cases  |
| Uterine suspensions and appendectomies | 14 cases |

voided, the average amount was 162 c.c., and the average time post-operatively of the first voiding was five hours and twenty minutes. For the untreated cases, of the 22 that voided normally, the average amount was 168 c.c., and the average time for first voiding was eight hours. These results confirm the findings of Woodruff and Te Linde and show that by means of this simple procedure the treated patients in five and one-half hours voided as much as did the controls in eight hours.

There were 39 patients in the treated series who had both a vaginal plastic and a laparotomy, and of these there were 34 (87 per cent) who voided spontaneously (17 had had a total abdominal hysterectomy). In the controls there were 23 cases, 11 (47 per cent) of whom voided. This series although smaller in number does indicate the efficacy of this procedure. These figures and the type of operation are shown in Tables V and VI.

TABLE V. OPERATIONS IN TREATED VAGINAL PLASTICS AND LAPAROTOMIES

|  |    |
|--|----|
| Vaginal plastic and total abdominal hysterectomy | 17 |
| Vaginal plastic and abdominal uterine suspension | 18 |
| Vaginal plastic and salpingectomy                | 4  |

TABLE VI. OPERATIONS IN UNTREATED VAGINAL PLASTICS AND LAPAROTOMIES

|  |   |
|--|---|
| Vaginal plastic and total hysterectomy           | 9 |
| Vaginal plastic and abdominal uterine suspension | 7 |
| Vaginal plastic and salpingectomy                | 7 |

The average amount of urine voided by the patients who were treated and had a vaginal plastic and laparotomy was 167 c.c., and in the untreated ones was 148 c.c. The average time of voiding in the treated patients was five hours and twenty minutes, while in the untreated ones it was ten hours. These figures show again that in the treated patients the bladder was more completely emptied in a considerably shorter time, thus preventing the occurrence of stasis and the resulting bladder infection that so commonly follows.

There was a total of 47 treated patients on whom various types of vaginal plastics were done, and 36 (76 per cent) voided following surgery and 11 (24 per cent) required one or more catheterizations. Of the 36 that voided, there were 24 on whom extensive work was done about the urinary bladder, most of them having a vaginal hysterectomy. Among the controls, of 44 cases there were 17 (40 per cent) that voided, while 27 (60 per cent) required one or more catheterizations. These figures do show that this procedure is of value where extensive vaginal

plasties are done. The type of operation performed is shown in detail in Tables VII and VIII.

TABLE VII. OPERATIONS IN TREATED VAGINAL PLASTICS

|  |    |
|--|----|
| Vaginal hysterectomy and anterior and posterior colporrhaphy | 16 |
| Manchester operation   | 7  |
| Anterior colporrhaphy and urethroplasty                      | 10 |
| Cervical operations  | 9  |
| Dilatation and curettage                                     | 5  |

TABLE VIII. OPERATIONS IN UNTREATED VAGINAL PLASTICS

|  |    |
|--|----|
| Vaginal hysterectomy and anterior and posterior colporrhaphy | 20 |
| Manchester operation   | 7  |
| Anterior colporrhaphy and urethroplasty                      | 12 |
| Cervical operations  | 7  |
| Dilatation and curettage                                     | 1  |

The average amount voided by the treated patients having a vaginal plastic was 186 c.c. which is more than that voided by those having a laparotomy. In the untreated ones, the average amount was only 70 c.c. or two and one-half times less than in the treated ones. The average time of voiding in the treated patients was six hours and forty minutes while in the controls it was seven hours.

There were three complications among the 114 treated patients. The most serious one was that of pelvic peritonitis which followed the removal of a cervical stump. After a rather stormy course the patient made a complete recovery. The second complication was one of gross hematuria that occurred on the second postoperative day in a patient that had a Manchester operation and perineorrhaphy. This condition was treated by means of bladder irrigations, using boric acid solution, and was completely cured after two days. The third was that of cystitis in a patient on whom a Le Fort colpocleisis had been done. This condition developed on the third postoperative day, and it is interesting to note that she had voided 100 c.c. shortly after surgery, but was catheterized on the third postoperative day after voiding and was found to have 150 c.c. of residual urine present. The presence of this residual urine undoubtedly contributed to the development of her infection. A complete recovery was made following bladder irrigations and urinary antiseptics.

In the untreated patients there were 15 who developed clinical cystitis from among the 97 who were operated upon. Every one of these were catheterized postoperatively. In 9 instances, the patients had had an extensive vaginal plastic and in 6 a vaginal plastic and a laparotomy. Pyelitis did not develop in any of these patients. These figures seem to indicate that bladder infections occur less frequently in the treated group.

comparison of ova Re-7950 and Al-7700 (Figs. 4 and 5) will show that, although the conceptuses are of about the same age and have apparently been on the endometrium the same period of time, the phase of endometrial development varies by as much as three days.

Even more striking is the discordance between Wi-8004 (Fig. 2) and Re-7950 (Fig. 4). Although the former is considered to be *two to three days younger* than the latter, the endometrium surrounding it is dated as *three days older* than that on which the much more advanced ovum is embedded.

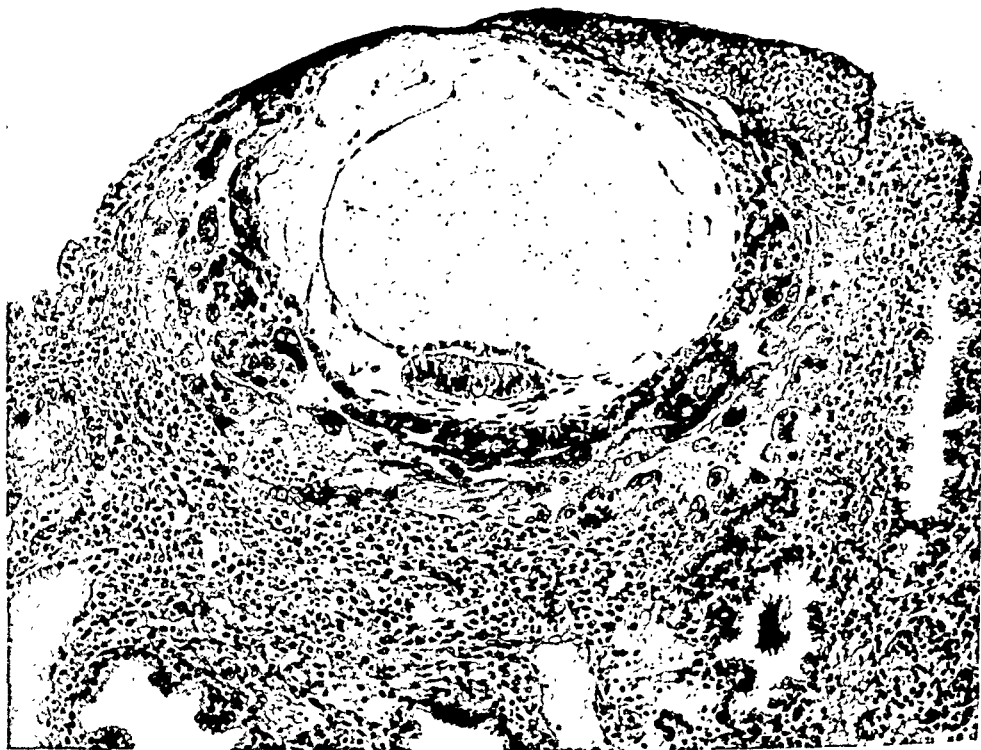


Fig. 5.—Al-7700. A 12.5-day human ovum embedded in twenty-six-day secretory endometrium. This specimen is less deeply implanted than the 9.5, 11.5, and twelve-day stages. The overlying endometrium is either very deficient or necrotic. The trophoblastic lacunae, constituting the future intervillous space of the placenta, are more prominent and contain more maternal blood than in the younger ova. The primordia of chorionic villi are seen in the four masses of proliferating cytotrophoblast located at "3," "4," "6," and "8 o'clock" respectively. The embryo is essentially the same as in the twelve-day specimen. Early decidual reaction about the ovum is slightly more prominent than in the 11.5-day specimen. Vascular response to the ovum is marked in the surrounding endometrium and appears in the form of large, dilated, thin-walled sinusoids. Endometrial glands are of actively secretory type. Hematoxylin and eosin.  $\times 100$ .

Ova Mu-8020 and Si-7699 (Figs. 1 and 3) are more nearly comparable. The former is *three to four days younger* than the latter, and the corresponding endometrium is in a phase dated *three days earlier*. Both these ova started embedment on a similar phase of endometrial development.

Not only may the endometrium vary at the time of nidation, but, as has already been stated, the conceptuses may vary in age from a minimum of five days to a maximum of perhaps even eight days at the time they start to invade the endometrium.

the histologic relationship of endometrium to trophoblast, nidation must have been started at least three days before; i.e., between the sixth and seventh postovulatory days, or between the twentieth and twenty-first days of a twenty-seven-day cycle. Study of these two conceptuses indicates that contact with the endometrium may be established as early as the fifth or sixth postovulatory day.

If we consider one of the older ova, Al-7700 (Fig. 5), which is regarded as being twelve to thirteen days old, we see it is still not completely covered, but the advanced relationship between the trophoblast



Fig. 4.—Re-7950. A twelve-day human ovum embedded in twenty-three-day secretory endometrium. The latter is at its peak of physiologic edema. The defect in the surface of the endometrium has not yet been completely repaired. The structure of the ovum is essentially the same as that of SI-7699 (Fig. 3), except that the lacunar network within the syncytiotrophoblast is more prominent. The exocoelomic cavity is a little larger and the embryo is located in the more usual position; i.e., directly at the embryonic pole instead of to one side, as in the former specimen. Hematoxylin and eosin.  $\times 100$ .

and the endometrium, as well as between the lacunae and the maternal vessels, indicates an attachment of more than three days, perhaps as many as five days. Thus nidation in this case might have occurred as late as the eighth day after ovulation; i.e., on the twenty-second day of a twenty-seven-day cycle.

Comparison of the estimated duration of embedment with the degree of endometrial development at the time of operation leads us to think either that nidation may occur on an endometrium exhibiting a variable degree of what has long been called "progestational" or "functional" activity, or else that the degree of ovular development may vary considerably at the moment nidation is started.\* For example,

\*That the former is more likely has already been suggested in a previous communication.<sup>4</sup>

per cent approaches accuracy, we must assume that additions to our collection will contain a smaller proportion of abnormal embryos, or that subsequent growth in those which appear abnormal would re-establish normal structure.

#### SUMMARY

1. Seven very young normal human conceptuses and five abnormal ones have been recovered from twelve of 60 excised uteri. One of the normal specimens, Mu-8020, estimated to be seven to eight days old (mean: 7.5) is, as far as we know, the youngest human embryo yet reported. The others range in age up to sixteen to seventeen days (mean: 16.5). By comparison of the age of the embryo with the associated endometrial histology, it is apparent that ovulation in two well-controlled cases occurred about fourteen (fifteen to thirteen) days before the anticipated dates of menstruation.

2. From a consideration of three ova estimated to be 7.5, 9.5, and 12.5 days old (mean values), we learn that nidation takes place at a variable age of the embryo, perhaps from the fifth to the eighth day of age, and on an endometrium which may vary in phase from the nineteenth to the twenty-second day of a twenty-seven-day cycle (catamenia on the twenty-eighth day).

3. The seven normal conceptuses were found on the posterior wall of the uterus, and the five abnormal ones on the anterior wall, probably a correlation which will not hold when more specimens are collected. The locus of nidation is not affected by the side on which the egg enters the uterus.

4. Five (42 per cent) of our twelve young embryos are so pathologic as to indicate probable early abortion. This figure (42 per cent) is of course higher than the percentage of abortions among diagnosed pregnancies. It is conceivable that more cases will show a lower proportion of defective ova. It seems likely from these findings, however, that either many pregnancies abort before recognition, during apparent normal menstruation, or that cytologic improvement takes place in some formerly abnormal conceptuses.

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The earliest likely attachment we have seen takes place when the endometrium is in the primary edematous stage with beginning glandular secretion (Mu-8020). The latest nidation of which we have evidence, in the three cases cited, apparently occurred only one to three days later (Al-7700). During this phase there is still much edema, but, toward the end of it, also swelling of the stroma cells around the hypertrophied spiral arterioles and just beneath the binding epithelium. In other words, nidation seems to take place on endometrium which is from nine to six days shy of a complete menstrual predecidua; i.e., between days nineteen and twenty-two of a twenty-seven-day cycle.

TABLE II. LOCATION OF IMPLANTATION SITES OF NORMAL AND ABNORMAL EMBRYOS

| CASE    | MEAN<br>ESTIMATED<br>AGE OF<br>OVUM<br>(DAYS) | OVARY<br>CONTAIN-<br>ING ACTIVE<br>CORPUS<br>LUTEUM | LOCATION OF IMPLANTATION SITE |                                  | CONDITION<br>OF OVUM |
|---------|---|---|-------------------------------|----------------------------------|----------------------|
|         |   |   | LATERAL<br>PLACEMENT          | ANTERIOR OR<br>POSTERIOR<br>WALL |                      |
| Mu-8020 | 7.5   | Right   | Nearer left                   | Posterior                        | Normal               |
| Wi-8004 | 9.5   | Right   | Right cornu                   | Posterior                        | Normal               |
| Si-7699 | 11.5  | Left  | Equidistant                   | Posterior                        | Normal               |
| Re-7950 | 12.0  | Right   | Nearer right                  | Posterior                        | Normal               |
| Al-7700 | 12.5  | Right   | Left                          | Posterior                        | Normal               |
| Ru-7801 | 13.5  | Right   | Nearer right                  | Posterior                        | Normal               |
| Bu-7802 | 16.5  | Right   | Left                          | Posterior                        | Normal               |
| Er-7850 | 11.5?   | Left  | Nearer right                  | Anterior                         | Abnormal             |
| Sm-8000 | 11.5?   | Left  | Left                          | Anterior                         | Abnormal             |
| Tr-7770 | 11.5?   | Right   | Right                         | Anterior                         | Abnormal             |
| Br-7800 | 13.0?   | Right   | Right                         | Anterior                         | Abnormal             |
| Be-7771 | —*  | Left  | —                             | Anterior                         | Abnormal             |

\*This specimen could not be dated due to the absence of the embryo.

### 3. THE LOCATION OF EMBEDMENT

Table II shows the location of the implantation sites in the several uteri, and, for comparison, the respective ovaries containing the active corpora lutea. Surprisingly, all the normal conceptuses were found implanted on the posterior wall of the uterus, whereas all those considered abnormal were located on the anterior wall. This may be a spurious relationship, but it is interesting, at least for the time being. There seems to be no correlation between lateral placement and the ovary of origin. Apparently, as in the monkey, the free blastocyst is passively moved about in the uterine cavity until it is able to attach itself. The duration of its stay in the uterus, and hence the age at which it enters, cannot be stated conclusively until after the recovery of free blastocysts, a difficult accomplishment.

### 4. THE FREQUENCY OF ABNORMAL OVA

Four of our twelve specimens are judged to have defective auxiliary structures; a fifth ovum, Be-7771, is certainly abnormal for it lacks the embryo. Hertig and Edmonds<sup>10</sup> have already demonstrated that the absence of all or most of the embryo is the commonest single finding in completed spontaneous abortions.

Five (42 per cent), then, of the 12 embryos are considered abnormal, thus giving evidence of inevitable abortion. If 42 per cent of pregnancies are aborted, many must be lost before the diagnosis of pregnancy is made, for it is computed that only about 8 per cent of diagnosed pregnancies are spontaneously aborted.<sup>11</sup> If this figure of 8

# THE EFFECT OF PROGESTERONE IN ADOLESCENT GIRLS AND YOUNG WOMEN WITH FUNCTIONAL UTERINE BLEEDING\*

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THE exact etiology of abnormal bleeding from the uterus, excluding that due to neoplasms, continues to be obscure. The increased knowledge of the reproductive cycle and our appreciation of the various means by which uterine bleeding can be produced experimentally in those mammals that menstruate, make it quite obvious that previous explanations, such as hyperestrinism, failure of ovulation, and ovarian deficiency do not fully explain all types of excessive and prolonged bleeding. Even the terms menorrhagia and metrorrhagia have lost their supposed differential significance because of the insistence of some gynecologists that bleeding due to breakdown of a nonprogestational endometrium is not menstruation. Failure of ovulation may, of course, result in hyperestrinism but the disturbances which result may be due to a deficiency of progesterone rather than to hyperestrinism. The only salient point seems to be that whenever the ovary is unable for any reason whatever to undergo periodically a cycle manifested by growth and rupture of a follicle, with formation of a normal corpus luteum, followed by normal involution of that corpus luteum, abnormal bleeding may occur. This, however, does not mean that abnormal bleeding always occurs whenever the ovary is unable to undergo an ovulatory cycle. Many fairly regular periods doubtless occur during adolescence, lactation, and the climacteric in the absence of ovulation without the appearance of excessive or prolonged bleeding. In fact, estrogen-deprivation of proper magnitude practically always results in menstruation. The complicating factor is progesterone. Progesterone-deprivation of proper magnitude also results in menstruation, and furthermore, even small amounts given for only a few days may result in progesterone-deprivation bleeding regardless of whether the endometrium shows progestational changes or not.

If it be true that prolonged and excessive bleeding, occurring especially in adolescent girls and young women, is associated with failure of ovulation, one might expect beneficial results from the use of pro-

\*Read, by invitation, at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.

## DISCUSSION

DR. WILLIAM E. STUDDIFORD, New York, N. Y.—The results which have been reported have been reached by a correlation of clinical facts with histologic study. This has resulted in the full utilization of a very limited supply of material. Such material might be more rapidly gathered if organized search for such specimens, under the direction of Dr. Rock, was carried out in institutions similar to the Free Hospital for Women in Brookline. While considered at Bellevue Hospital, the idea was abandoned because of the lack of opportunity for the prolonged study of the patient while on a preoperative waiting list. Without the accumulation of the necessary clinical facts, the mere collection of the specimens would not be of any great value.

A more rapid accumulation of such early embryos might serve to reinforce or modify certain of the observations made on the basis of the present series. The estimation of the probable time of ovulation coincides fairly closely with the present clinical beliefs. Might not study of augmented material reveal occasional wider variations in this time? The question of duration of the functional capacity of spermatozoa in humans can only be answered in further studies. Certain experimental studies in animals suggest that their function shows a sharp decrease after twenty-four hours.

Most remarkable is the occurrence of 42 per cent abnormal embryos, apparently doomed to abortion, a figure much higher than the accepted abortion rate. With the accumulation of a larger series, is it not probable that this percentage will decrease? No more understandable is the preference of the abnormal ovum for the anterior wall of the uterus. Here it would seem certain that a larger series would prove such a conclusion to be in error.



short line just above the indicated amount. All amounts over 100 mg. represent anhydrohydroxy progesterone given orally, and all amounts under 100 mg. represent progesterone given intramuscularly. When the indicated amount was between 20 and 40 mg., the daily amount was 5 mg., and when the total amount was more than 40 mg. and less than 100 mg., the daily dose was 10 mg. In the few instances in which less than 20 mg. were given, the daily dose was usually 2.0 mg.

From an inspection of the charts, it is evident that in many instances essentially normal menstrual periods occurred for several months after a single course of injections. In other cases the bleeding ceased either

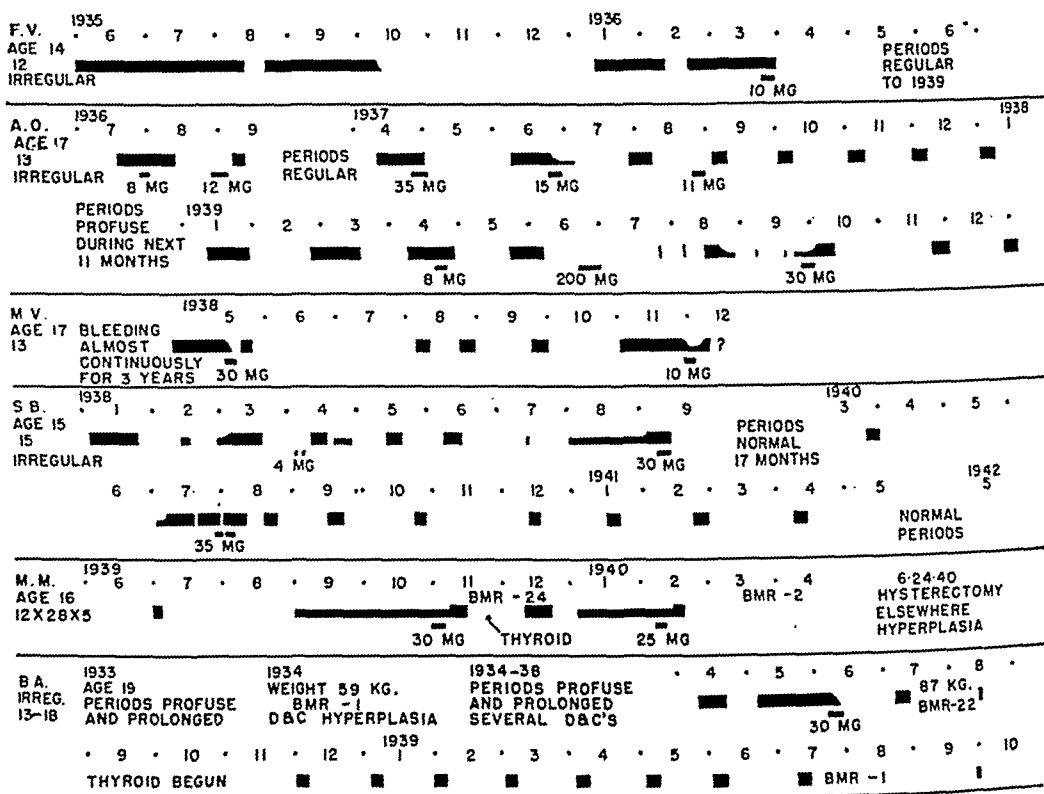


Fig. 1.

Figs. 1 to 5.—Detailed chronologic record of the periods of bleeding and the therapy utilized.

during the injections or within a few days after the injections, but prolonged bleeding recurred again within a few weeks. In still other cases the bleeding was interrupted only to be followed by amenorrhea for many weeks. When the larger doses of progesterone or of anhydrohydroxy progesterone were given, there was usually an increase in bleeding, beginning about forty-eight hours after the discontinuation of the hormone and lasting for about five or six days. In most instances this progesterone-deprivation bleeding was not excessive, but occasionally the bleeding was considerably more than the subject ordinarily experienced during a menstrual period.

gesterone. If the bleeding be due to hyperestrinism, progesterone should result in a decrease in the hyperestrinism, even though the amount of estrogen being produced remains unaltered. Also after a course of treatment with adequate amounts the endometrium should break down and be shed as during menstruation following an ovulatory cycle. This by itself should be beneficial, since it should result in the destruction of a hyperplastic endometrium. Progesterone might also be expected to have an effect on the pituitary, perhaps decreasing the output of follicle-stimulating hormone. Follicle growth is ordinarily relatively suppressed when corpus luteum activity is greatest, probably because of inhibition of the pituitary, and hence the administration of progesterone might be expected to produce an effect on the pituitary similar to that brought about by activity of the corpus luteum itself. With these thoughts in mind we have treated a group of patients with progesterone and anhydrohydroxy progesterone.\*

Progesterone has already been used by numerous investigators for the treatment of functional uterine bleeding, although the results have not been consistent (see Hamblen, 1942). Increased bleeding has been sometimes observed (Hamblen, 1936) whereas improvement has also been observed (Clauberg, 1932; Knab, 1933; Lauterwein, 1940; Wenner, 1940; Wiesbaden, 1941; Wilson, 1936).

The general plan of treatment was to withhold therapy until bleeding had been in progress for two weeks or more. Progesterone was then given daily by intramuscular injection for a period of four to eight days. In the earlier observations only 2 mg. were given daily but, as the hormone became more readily available, the dose was increased to either 5 or 10 mg. daily. Anhydrohydroxy progesterone (ethinyl testosterone, pregnenolone) has been given orally to several patients. The amount given has varied from 180 mg. to 600 mg., but in general the total dose was given over a period of from four to eight days. In those cases in which there was anemia, some form of iron, usually ferrous sulfate, was given. The basal metabolic rate was determined in the majority of the cases at some time during the period of observation. Desiccated thyroid, however, was not given initially to any of the patients until after the effect of progesterone had been observed. In some cases abnormal bleeding occurred while thyroid was being given and in them the thyroid was continued at the same level while the effect of progesterone was being observed.

The detailed menstrual records and the pertinent data concerning therapy are shown in the charts. The duration of bleeding is shown by the broad black lines or squares. The height of the black band does not accurately indicate the amount of bleeding, except that the narrower bands and smaller squares indicate bleeding described by the subject as being scant. The duration of medication is indicated by the

\*The progesterone and anhydrohydroxy progesterone used in this study were furnished by The Schering Corporation, Bloomfield, N. J.

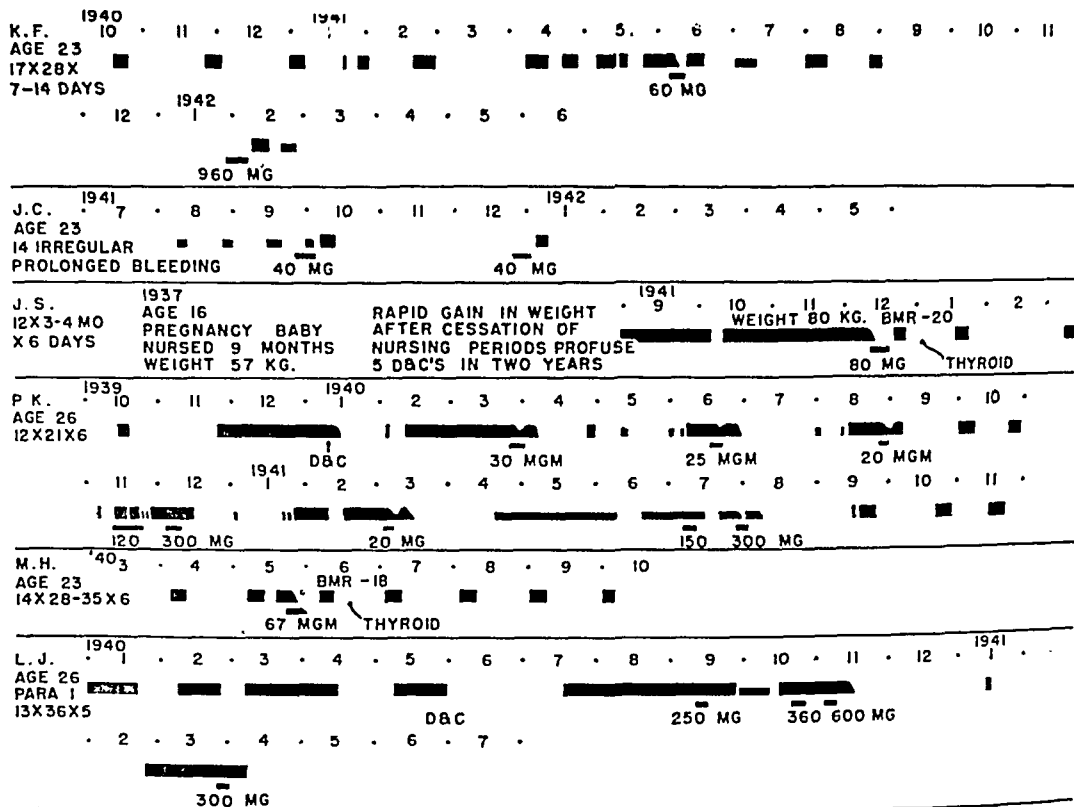


Fig. 4.

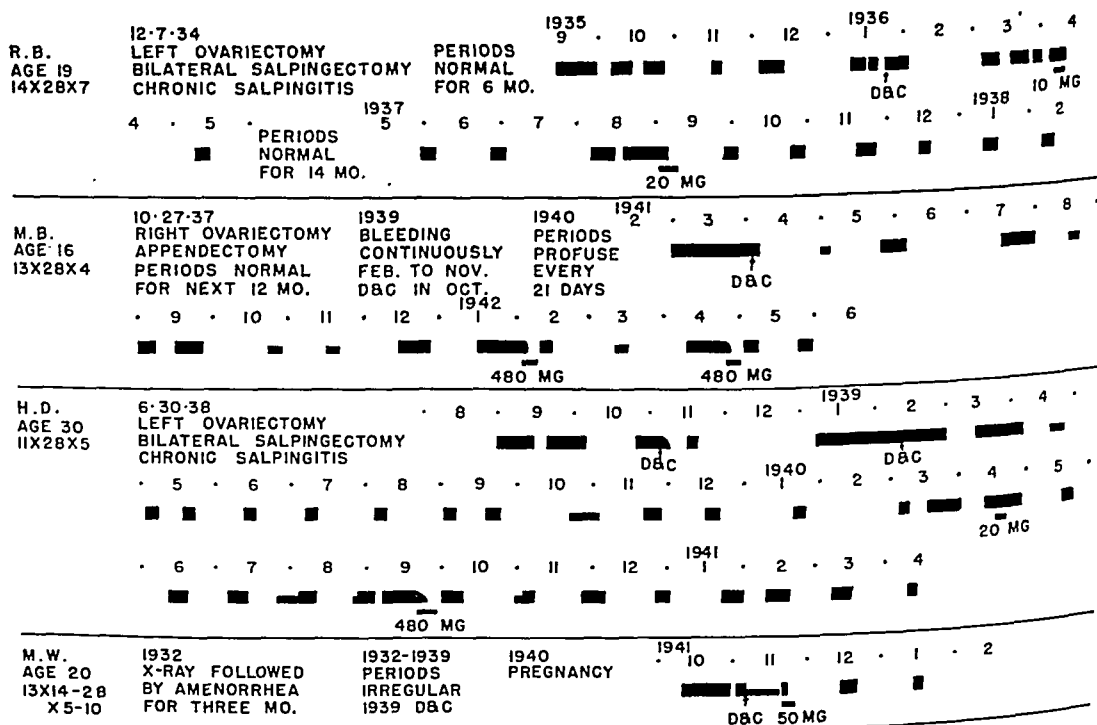


Fig. 5.

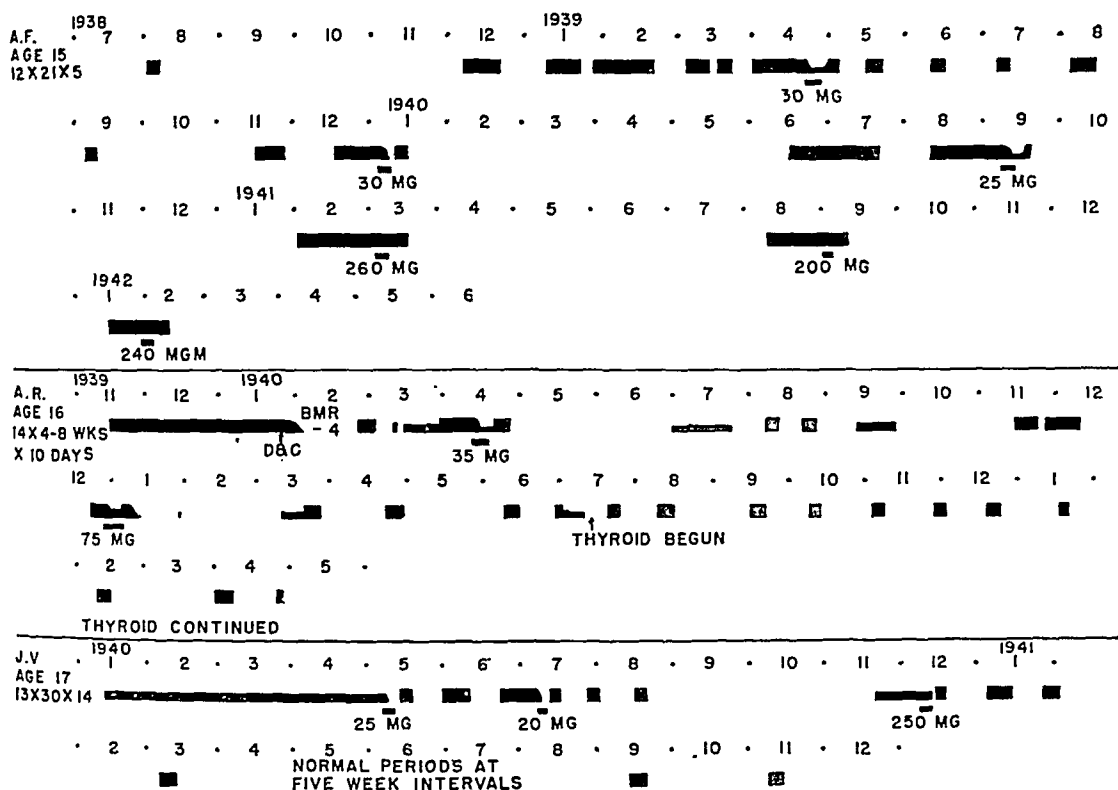


Fig. 2.

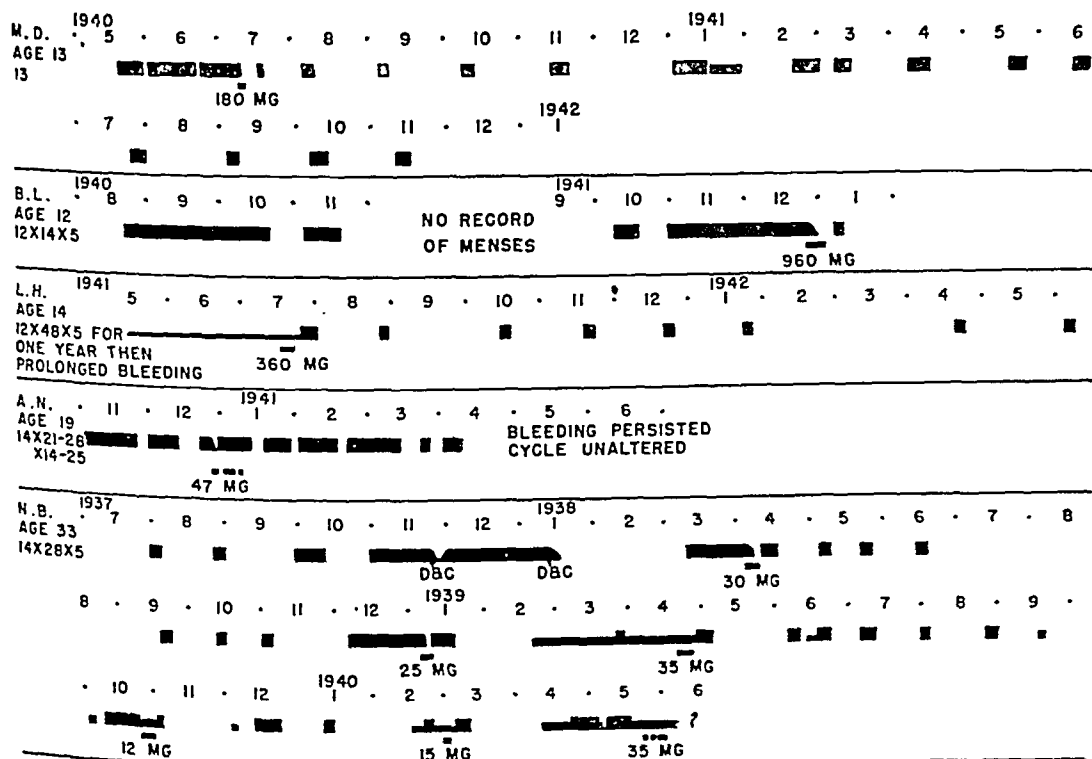


Fig. 3.

## SUMMARY AND CONCLUSIONS

One hundred and fourteen patients on whom various gynecologic operative procedures were performed received a bladder instillation of 1 ounce of a 0.5 per cent aqueous solution of mercurochrome, postoperatively to avoid catheterization, and of these, 93 (81 per cent) voided spontaneously. In 97 untreated patients handled by the same surgeon, only 45 (47 per cent) voided normally. In the instance where a laparotomy only was done, 82 per cent voided normally in the treated group, while in the controls there were only 73 per cent. The treated patients who had laparotomies voided as much urine in five and one-half hours as did the controls in eight hours; demonstrating that by the use of this simple aid the patient was able to more completely empty the bladder in a shorter time.

Among the treated patients who had both a vaginal plastic and a laparotomy, 87 per cent voided, as compared with 47 per cent in the untreated ones. They also voided more urine in five hours than did the controls in ten hours.

For those having a vaginal plastic, 76 per cent voided among the treated group, while among the controls only 40 per cent. Here again more urine was passed in the treated group and in a shorter time.

Among the treated patients there were three complications, while in the controls 15 patients had complications; all being cystitis.

This simple procedure has, in the author's opinion, brought about a more comfortable convalescence with fewer complications and is now used routinely on his service.

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Byron, F. X., and Welch, C. Stuart: A Complication From the Use of Glove Powder, Surgery 10: 766, 1941.

Nodules in operative scars sometimes present interesting problems. Commonly, they are due to malignant implants or metastases or foreign bodies, such as suture material. In some cases, tuberculosis or endometriosis is found. In this communication the writers call attention to the importance of talcum powder as a causative factor not only of nodules in skin and subcutaneous tissue of abdominal incisions but also of tubercle-like lesions of the peritoneum. During the last year, the authors have observed several such instances. Small nodules, often tender to pressure or even painful, were discovered consisting of miliare granulomatous lesions resembling tubercles. They describe in detail four cases and offer several microphotographs showing the histopathologic pictures of foreign body giant cells containing talc crystals.

It seems obvious that gloves after being put on should be carefully washed in a hand basin.

HUGO EHRENFEST.

The data presented in the charts have been studied to ascertain, if possible, how much effect the progesterone has really had on the course of the disease in these patients. The duration of bleeding before therapy has been contrasted with the duration of bleeding after therapy. For this study five consecutive periods have been considered. The first period (days 1 to 30) is one of thirty days in which no therapy was given. In many instances the amount of bleeding in this period was negligible because of the frequent occurrence of amenorrhea prior to abnormal bleeding. The second period of thirty days (days 31 to 60) followed the first period and was terminated on the last day of therapy. These two periods in reality cover the period of sixty days immediately preceding the last day of therapy, and any bleeding occurring during these periods represents bleeding unaltered by therapy, except as it may have been influenced by the short period of therapy. The third period (days 61 to 70) is of only ten days. Since progesterone-deprivation frequently is followed by a menstrual period, it seemed necessary to separate any bleeding which may have occurred for this reason from bleeding which occurred subsequently. The fourth period (days 71 to 100) covers the first thirty days after the time when progesterone-deprivation bleeding should have been completed and the fifth and final period (days 101 to 130) covers the next thirty days. By grouping the data in this manner it is possible to compare the duration of bleeding in two consecutive periods of thirty days each before (and including) therapy with the duration of bleeding in two consecutive periods of thirty days each after the cessation of therapy, the periods before and after therapy being separated by a period of ten days in which bleeding may have occurred as a result of withdrawal of the hormone.

The data have been further rearranged into three groups. In the first group (Table I), the observations are listed in which the menstrual periods were essentially normal for four months or more after

TABLE I. SUMMARY OF OBSERVATIONS IN WHICH THERAPY WAS FOLLOWED BY NORMAL MENSES FOR FOUR OR MORE MONTHS

| SUBJECT  | BLEEDING DURING DAYS |       |                    |       |        |         | NORMAL PERIODS MONTHS | RECURRENT |
|----------|----------------------|-------|--------------------|-------|--------|---------|-----------------------|-----------|
|          | 1-30                 | 31-60 | PRO-GESTERONE* MG. | 61-70 | 71-100 | 101-130 |                       |           |
| F. V.    | 20                   | 30    | 10                 | 0     | 5      | 5       | 36                    | No        |
| A. O.    | 6                    | 14    | 8                  | 10    | 5      | 6       | 8                     | Yes       |
|          | 0                    | 22    | 15                 | 6     | 10     | 5       | 6                     |           |
|          | 14                   | 10    | 30                 | 9     | 0      | 8       | 6+                    |           |
| S. B.    | 13                   | 30    | 30                 | 0     | 5      | 5       | 17                    |           |
|          | 5                    | 28    | 35                 | 5     | 6      | 7       | 24                    |           |
| A. F.    | 15                   | 28    | 30                 | 7     | 7      | 8       | 4                     | Yes       |
| J. V.    | 0                    | 23    | 250                | 4     | 10     | 7       | 12                    |           |
| M. D.    | 22                   | 27    | 180                | 3     | 5      | 4       | 6                     |           |
| L. H.    | 30                   | 30    | 360                | 9     | 3      | 0       | 11                    |           |
| R. B.    | 8                    | 20    | 10                 | 0     | 6      | 6       | 14                    | Yes       |
|          | 5                    | 23    | 20                 | 0     | 6      | 6       | 7                     |           |
| N. B.    | 30                   | 30    | 35                 | 8     | 1      | 15      | 4                     | Yes       |
| H. D.    | 9                    | 20    | 20                 | 7     | 5      | 8       | 4                     | Yes       |
|          | 15                   | 23    | 480                | 8     | 8      | 9       | 6                     |           |
| Q. M. H. | 6                    | 15    | 67                 | 5     | 7      | 7       | 4                     |           |
| Average  | 12.4                 | 23.3  |                    | 5.0   | 5.6    | 6.6     |                       |           |

\*Progesterone or anhydrohydroxy progesterone, therapy ending sixth day (see text).

the use of progesterone. In the second group (Table II), the observations are listed in which there was a recurrence of abnormal bleeding in less than four months, and in the third group (Table III) are listed the observations in which amenorrhea followed either immediately or after two or three menstrual periods. In addition to the cases given are eight observations in which the follow-up has been for less than four months. In each of these untabulated cases there was cessation of bleeding but the subsequent course was either unknown or the therapy had been too recent for adequate observation.

TABLE II. SUMMARY OF OBSERVATIONS IN WHICH THERAPY WAS FOLLOWED BY RECURRENCE OF ABNORMAL BLEEDING WITHIN FOUR MONTHS

| SUBJECT | BLEEDING DURING DAYS |       |                   |       |        |         | RECURRENCE AFTER WEEKS |
|---------|----------------------|-------|-------------------|-------|--------|---------|------------------------|
|         | 1-30                 | 31-60 | PROGESTERONE* MG. | 61-70 | 71-100 | 101-130 |                        |
| A. O.   | 5                    | 20    | 35                | 0     | 0      | 24      | 6                      |
|         | 21                   | 17    | 8                 | 8     | 13     | 2       | 4                      |
| J. V.   | 30                   | 27    | 25                | 5     | 11     | 22      | 6                      |
| P. K.   | 20                   | 30    | 30                | 6     | 4      | 8       | 8                      |
|         | 7                    | 18    | 25                | 8     | 1      | 19      | 7                      |
|         | 0                    | 19    | 20                | 6     | 7      | 6       | 10                     |
|         | 6                    | 24    | 300               | 5     | 1      | 19      | 6                      |
|         | 14                   | 23    | 20                | 9     | 0      | 28      | 6                      |
| M. B.   | 13                   | 20    | 480               | 5     | 5      | 10      | 9                      |
| M. M.   | 30                   | 30    | 30                | 10    | 5      | 19      | 8                      |
|         | 19                   | 30    | 25                | 8     | 0      | ?       | 8                      |
| A. N.   | 25                   | 21    | 47                | 6     | 26     | 23      | 2                      |
| N. B.   | 5                    | 28    | 25                | 9     | 0      | 19      | 6                      |
|         | 3                    | 25    | 12                | 4     | 2      | 11      | 12                     |
|         | 5                    | 16    | 15                | 8     | 2      | 30      | 4                      |
| L. J.   | 28                   | 31    | 250               | 10    | 25     | 30      | 1                      |
| Average | 14.4                 | 23.7  |                   | 6.7   | 5.4    | 18.0    |                        |

\*Progesterone or anhydrohydroxy progesterone, therapy ending sixtieth day (see text).

TABLE III. SUMMARY OF OBSERVATIONS IN WHICH THERAPY WAS FOLLOWED BY AMENORRHEA

| SUBJECT | BLEEDING DURING DAYS |       |                   |       |        |         | AMENORRHEA WEEKS | RECURRENCE |
|---------|----------------------|-------|-------------------|-------|--------|---------|------------------|------------|
|         | 1-30                 | 31-60 | PROGESTERONE* MG. | 61-70 | 71-100 | 101-130 |                  |            |
| B. A.   | 16                   | 29    | 30                | 0     | 6      | 2       | 12†              |            |
| A. F.   | 12                   | 22    | 30                | 5     | 0      | 0       | 22               | Yes        |
|         | 10                   | 30    | 25                | 7     | 0      | 0       | 19               | Yes        |
|         | 7                    | 30    | 260               | 8     | 0      | 0       | 21               | Yes        |
|         | 0                    | 26    | 200               | 6     | 0      | 0       | 17               | Yes        |
|         | 0                    | 19    | 240               | 7     | 0      | 0       | 17+              |            |
| A. R.   | 13                   | 30    | 35                | 9     | 0      | 0       | 9                | Yes        |
|         | 19                   | 19    | 75                | 7     | 1      | 0       | 8                | No         |
| J. V.   | 16                   | 17    | 20                | 5     | 10     | 0       | 10†              | Yes        |
| K. F.   | 16                   | 21    | 60                | 7     | 9      | 9       | 36+†             |            |
| J. C.   | 8                    | 9     | 40                | 6     | 0      | 0       | 36+              |            |
| L. J.   | 25                   | 26    | 600               | 8     | 0      | 3       | 8                | Yes        |
| M. V.   | 30                   | 28    | 30                | 5     | 0      | 0       | 9                | Yes        |
| N. B.   | 0                    | 28    | 30                | 6     | 5      | 10      | 13†              |            |
| Average | 12.3                 | 23.8  |                   | 6.1   | 2.2    | 1.7     |                  |            |

\*Progesterone or anhydrohydroxy progesterone, therapy ending sixtieth day (see text).

†2 or 3 periods before amenorrhea began.

Observations in which the amount of progesterone given was less than 8.0 mg. (S. B.) or in which progesterone was given when the patient was not bleeding (A. O.; K. F.; J. C.) are not tabulated. Three observations with anhydrohydroxy progesterone are not tabulated. The doses used in one subject (P. K.), 120 mg. and 150 mg., are small and in both instances they were followed by larger doses so that the course immediately following was complicated by added therapy. The other untabulated observation (L. J.) was with 360 mg., but this was followed soon by 600 mg.

The general impression gained from this study is that in about one-third of the instances the menstrual periods remained essentially normal for many months after a single course of progesterone or anhydrohydroxy progesterone, whereas in another third of the instances there was a recurrence of abnormal bleeding in less than four months. In the remaining third the bleeding ceased but amenorrhea ensued. However, even in those cases in which there was a recurrence of bleeding within thirty to sixty days there seems to have been a significant reduction in the amount of bleeding taking place in the first thirty days of the follow-up period (days 71 to 100).

The average duration of bleeding in the first period (days 1 to 30) was essentially constant for all three groups of cases, about thirteen days, and similarly the average duration for the second period (days 31 to 60) was the same, about twenty-three days. These averages serve as adequate evidence that abnormal bleeding had been present for a considerable time before treatment was begun. The amount of bleeding which occurred during the third period (days 61 to 70) was about the same for all groups, about six days. From this time on, however, the reactions of the various groups are somewhat different. There was little difference in the fourth period (days 71 to 100) between those instances when normal cycles followed for at least four months (Table I) and those instances in which recurrence was to take place within four months (Table II), the average duration in this period being 5.6 and 5.1 days, respectively. There was no indication during the first month after therapy of what the future behavior was to be. In the instances in which amenorrhea followed therapy, the bleeding was considerably less, since many times the amenorrhea immediately followed the period of withdrawal bleeding. In the last period (days 101 to 130), there is an even more noticeable difference between the groups. In those instances in which normal cycles persisted (Table I), the average duration of bleeding was only 6.6 days, whereas in those instances in which recurrence had taken place (Table II) the average duration of bleeding was 17.1 days. This was almost as much as in the thirty-day period prior to and including treatment.

There is one other point which should be noted. In virtually every instance bleeding ceased (including withdrawal bleeding) within ten days of the discontinuation of therapy. The subsequent course varied



to be sure but in all instances but one (A. M.) the pattern of bleeding was measurably and significantly altered.

The effect of progesterone on the endometrium itself has not been studied in this group of cases. Many of the subjects were adolescent girls, and it was thought inadvisable to subject them to the discomfort of biopsy of the endometrium. Diagnostic curettage was done in only a few cases, but in all of those in which it was done, the endometrium showed varying degrees of hyperplasia.

#### DISCUSSION

The mechanism whereby progesterone alters the pattern of bleeding is not entirely clear. There is no difficulty, of course, in explaining the bleeding which occurs following the administration of the hormone, for it is well established that progesterone-deprivation is ordinarily followed by breakdown of the endometrium and bleeding (see Corner, 1939). This is the usual explanation for the course of events in the ovulatory cycle. Furthermore, the endometrium does not necessarily have to be in the late premenstrual phase for progesterone deprivation to produce bleeding. The administration of progesterone for only three or four days in the first half of the cycle may result in bleeding, even though the duration of injections is not long enough for the endometrium to show progestational changes. Even in patients with secondary amenorrhea, bleeding can be induced by the injection of progesterone for only a few days (Zondek and Rozin, 1938). In the observations reported here, there was an increase in bleeding in many instances, beginning about forty-eight hours after cessation of therapy. These patients responded in an essentially normal manner, therefore, to progesterone-deprivation. This breakdown of the endometrium is undoubtedly just as effective as a curettage in so far as interruption of bleeding is concerned. In every instance but one, there was complete interruption of bleeding for a time at least.

The course of events, after the initial deprivation bleeding had occurred, is more intriguing. In those instances where normal cycles occurred for many months, it is obvious that the disturbance in ovarian activity, which is assumed to be responsible for the abnormal bleeding, was fundamentally changed. The change from abnormal bleeding to normal cycles was so abrupt that it seems unlikely that it was due to pure chance. It seems probable, also, that this change was brought about by a change in the activity of the pituitary. Estrogens are known to affect the pituitary, although there is a difference of opinion concerning the effect; some experiments indicate inhibition and other experiments indicate stimulation.

If it be assumed that estrogen inhibits the pituitary, the following explanation would appear logical. The ovary is stimulated to a certain point, but inadequately for ovulation to occur. This results in the

continuous production of estrogen which in turn may inhibit the pituitary so that the amount of gonadotropic hormone being elaborated is never quite adequate to induce ovulation. This results either in amenorrhea or prolonged bleeding, conditions present in this type of patient. When progesterone is given, the estrogen is inhibited and consequently the pituitary is released from inhibition by the estrogen so that it may produce a quantity of gonadotropic hormone adequate to induce ovulation, in which event a normal ovulatory cycle ensues.

Another explanation can be developed from the fact that follicular growth is relatively suppressed by the presence of functional corpora lutea. Mammals which ovulate spontaneously do not ovulate when functional corpora are present nor do those animals which require the stimulus of mating (such as the rabbit) ovulate following mating when functional corpora are present. In fact, the administration of progesterone to the rabbit prevents ovulation following mating, apparently because the pituitary is unable to release gonadotropic hormone under these conditions (Makepeace, Weinstein and Friedman, 1938; Friedman, 1941). One might suppose, therefore, that progesterone itself, in the cases under discussion, had suppressed the production of gonadotropic hormone sufficiently so that the ovary was not being stimulated. This should result in widespread follicular atresia and hence in a reduction in the amount of estrogen being produced. Then, as the pituitary escaped from its inhibition by progesterone, it might produce gonadotropic hormone at a more rapid rate and hence stimulate the ovary sufficiently so that ovulation could take place.

The explanation of the observation that recurrence may take place within two or three months, or that amenorrhea may ensue is not so involved. If one assumes that progesterone in these cases had had no effect on the fundamental ovarian dysfunction, the result is precisely what would be expected. Progesterone-deprivation probably leads to a fairly complete breakdown of the endometrium, and consequently the hyperplastic endometrium was eradicated, the result being the equivalent of a curettage. The subsequent behavior would, of course, be essentially the same as before therapy except that it ordinarily requires several weeks before the endometrium becomes sufficiently hyperplastic to result in excessive bleeding.

The amount of progesterone used and the duration of therapy are such that the procedure is quite simple. It is only necessary to give about 5 mg. daily for six days. It is probably important, however, to give the hormone every day, not every second or third day. Progesterone is apparently rapidly absorbed and metabolized since deprivation bleeding ordinarily begins within forty-eight hours. The omission of a single injection may, therefore, result in a significant reduction in the amount of hormone being made available. The amount of anhydrohydroxy progesterone necessary to produce an effect similar

to 25 to 50 mg. of progesterone is not evident from this study. However, deprivation bleeding occurred when 80 mg. or more were given daily for five or six days.

It is of interest that there were many recurrences of abnormal bleeding in this group of cases. It seems probable, therefore, that prolonged bleeding, once it has been observed in a given subject, is highly indicative of the presence of a fundamental defect in the pituitary-gonadal relationship. Whether or not this disturbance is irreparable can only be determined by prolonged observation and therapy by the trial and error method. Thyroid may be very helpful in a small proportion of the cases. In two cases of the present series there was marked improvement when thyroid was given. Whether or not these subjects will mature into normal women capable of childbearing remains to be seen. One cannot refrain, however, from supposing that the disturbance in ovarian function present in these individuals is very similar to the disturbance in ovarian function observed in a certain strain of rats (Wolfe, Burack and Wright, 1940) that have a fundamental defect in their ovulating mechanism. These rats have periods of persistent estrus, due to persistence of follicles and failure of ovulation, interspersed with periods of anestrus in which there is more cornification of the vagina than usual. In addition the fertility is low. But more important, this disturbance in the pituitary-gonadal relationship is apparently hereditary. Similarly, there is a strain of mice which has a hereditary defect, resulting in a pituitary which has no eosinophiles. These mice are deficient in growth hormone and consequently remain dwarfed unless given anterior pituitary implants as extracts (Smith and MacDowell, 1930). If the inability of these individuals to ovulate regularly is a hereditary or congenital characteristic it would perhaps be unwise to attempt to induce ovulation, even were it possible to do so, since if followed by pregnancy it would tend to increase the number of individuals with the defect.

Ovarian deficiency may, of course, be produced surgically. In this study, there were four subjects in whom functional uterine bleeding developed soon after the removal of one ovary. This is not surprising since removal of one ovary and part of the remaining ovary in some rodents (rats, rabbits, and guinea pigs) disrupts the pituitary-gonadal relationship so much that ovulation fails to occur and a state of continuous estrus occurs. In the unilaterally castrated individuals reported here, progesterone seems to have been beneficial since in each case normal cycles followed the therapy for several months.

#### SUMMARY

The detailed menstrual records of 24 adolescent girls and young women with functional uterine bleeding are given. These subjects were given progesterone or anhydrohydroxy progesterone, and the effect on the menstrual pattern was observed over a period of many

months in most cases. In general, the administration of approximately 30 mg. of progesterone was followed by cessation of bleeding within ten days of the last injection. Progesterone deprivation bleeding occurred frequently, thereby explaining the bleeding occurring in the first few days after therapy. In about one-third of the observations, normal cycles occurred for four months or more after therapy, whereas in another third there was a recurrence in less than four months. Even in these, however, there was no recurrence in the first month. In the final third of the observations, amenorrhea followed immediately or after two or three cycles.

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#### DISCUSSION

DR. EMIL NOVAK, BALTIMORE, MD.—I do not believe that anyone is altogether satisfied with the results of organotherapy for functional bleeding. There are various reasons for this, among them is the fact that many seem to look upon functional bleeding as a single entity, and to fit all cases into one clinical and therapeutic mold. As a matter of fact, it is quite certain that the endocrine imbalance differs very much in different cases, both qualitatively and quantitatively, and our present methods do not always equip us for intelligent appraisal of each case on its individual merits.

Either the ovulatory or the anovulatory type of cycle may undergo aberrations which express themselves clinically as functional bleeding. The anovulatory, which may perhaps be considered the more primitive type, is more prone to upsets than the ovulatory, and it is this broad variety of dysfunction which is concerned in the so-called metropathia hemorrhagica of Schröder, and which is represented by the cases reported today by Dr. Allen.

One obvious comment on this paper must be that the patients reported are all very young, at least 13 of the 24 being between twelve and seventeen, inclusive. There is no doubt that in many young girls functional bleeding corrects itself, through the spontaneous establishment of ovulation, without any treatment. It would probably be possible to collect a series of the same size, with as many cures, without any organotherapy. Nor are the results better than many have reported with other hormonal methods, such as androgenic therapy.

This is not a criticism of the employment of progesterone, which is certainly as rational as any other plan, and which I also employ frequently. But there is still much to learn as to the role of progesterone in the cycle. It has physiologic properties not always easy to reconcile. Its deprivation brings about the menstrual bleeding of the ovulatory cycle; its injection in the first half of the intermenstruum brings about bleeding from an endometrium which is not progestational;

it has been shown by Hartman and Speert that in the castrated monkey, contrary to the former view, it can bring about a progestational endometrium without preliminary priming with estrogen; it undoubtedly plays a part in estrogen partition as Smith and Smith have shown; and so on.

Dr. Allen has endeavored to bring about progestational changes in the endometrium, and this is certainly possible, as many investigators have shown. But it is not certain that full progestational effects are always necessary to bring about correction of abnormal bleeding. Indeed, good results have been reported by many with much smaller dosage, although it must be admitted that many of these reports are uncritical. The physiologic effects of hormone injections do not necessarily parallel the histologic.

Finally, even though progestational effects are produced, it does not necessarily follow that the pituitary function can be beaten into a cyclic submission by regular repetitions of this highly expensive treatment. The mere existence of functional bleeding of this type presupposes a disordered and perhaps unresponsive pituitary.

Instead of injecting various hormones and attacking the problem peripherally, the as yet purely utopian ideal would be to nurse the ailing gland back to normal in some fashion or other. Aside from constitutional measures, it is possible that recent investigations on the relation of certain vitamin factors to the hormones may prove helpful. Allen and Figge have recently shown the apparent importance of the pantothenic acid factor in the production of the gonadotropic hormones by the pituitary, and Dr. Figge and I are now endeavoring to apply this observation clinically, although it is too early to speak of results.

DR. JEAN PAUL PRATT, DETROIT, MICH.—The problem considered by Dr. Allen is complex because functional bleeding is, as yet, unsatisfactorily explained. We know too little about the causes of the cycle in normal menstruation. Accepting the ovary-pituitary relationship, we must still determine what influences the pituitary. To what extent do the thyroid and other glands of internal secretion influence the pituitary?

The endocrine glands are functionally related to each other, to the autonomic nervous system, to the general state of health, to the level of nutrition, to the age of the patient, to the emotions and to the environment. It is essential, therefore, to approach this special problem by a consideration of the patient as a whole. This broad view does not preclude the investigation of special features, but it does help to keep the proper balance in the interpretation of accumulated data. The studies on progestin are commendable for even if they do not provide the answer to the treatment of functional bleeding, they contribute to our fundamental knowledge of this complex subject.

DR. JOE V. MEIGS, BOSTON, MASS. (By Invitation).—In our clinic in the Massachusetts General Hospital we have been using a method similar to Dr. Allen's and our results have been about like his. We feel that in the younger age group we have been able to relieve about 50 per cent of our patients. A good many of the older group were also relieved.

We have had patients who have been vitamin deficient. In one case a young girl with scurvy had eaten good food at home, but when away at school she ate ice cream, soda, candy, and cake instead of regular meals. She began to bleed abnormally and when she returned home there was direct evidence of scurvy.

DR. GEORGE VAN S. SMITH, BROOKLINE, MASS.—From our studies of estrogen metabolism in functional uterine bleeding, Mrs. Smith and I are convinced that an adequate amount of progesterone constitutes specific therapy, not only for the bleeding itself but also, in cases before the menopausal years, for the endocrine dysfunction which is responsible for this bleeding. The partition of the urinary

estrogens before and during this type of flow reflects a complete absence of luteal control. The administration of adequate progesterone not only stops the flow, but alters the partition of the urinary estrogens in the direction of what is found during the luteal phase of a normal cycle. Urinary findings at the start of the artificially induced period which follows progesterone are similar to those at the start of a normal postovulatory catamenia. It is because of this latter effect, namely the reproduction of a normal progestin-withdrawal bleeding, that we believe spontaneous ovulatory cycles are observed to occur in cases of functional flowing following adequate progesterone treatment. Our studies indicate that progestin-withdrawal flow is associated with a sudden increase in the rate of estrogen destruction which is not found at the start of simple estrogenic bleeding. We have come to the conclusion that progestin-withdrawal bleeding, with its associated sudden increase in estrogen destruction, provides a necessary synergistic stimulus, which I have already described, for the normal growth and maturation of the ovarian follicle.

My own clinical experience with 11 cases to date supplies the strongest support for these deductions from our laboratory findings. My present treatment for typical functional flowing is as follows: First, the bleeding is stopped with progesterone, which in a severe case may require 25 mg. a day for five days. Two to four days later another flow will begin. Counting the start of this progestin-withdrawal flow as day one, I begin on the twenty-first day a series of five daily injections of 10 mg. of progesterone plus 0.5 mg. of estradiol. The last injection is given on day 25 and three to five days later a period, normal in amount and duration, occurs.

One patient, whose functional flowing, beginning at puberty twelve years ago, had failed to respond to all conservative medical and surgical measures for eight years, was treated by this method. After 7 cycles of the above therapy she has had regular menstruation from secretory endometrium since October, 1941. Estrogen studies throughout the months of treatment indicated that spontaneous luteal secretion in this case did not begin until after the first two cycles of treatment, and did not reach the normal postovulatory level until after the last cycle of artificially induced menstruation. This was undoubtedly as recalcitrant a case as one would ordinarily encounter. From Dr. Allen's observations it would appear that repeated treatment is not necessary in all cases.

I have yet to discover whether or not spontaneous ovulatory cycles may be established consistently by this means in women with functional uterine bleeding under the early forties, or how long they will continue after cessation of treatment. At least I can tell patients when they are going to flow and how long it will last, so long as I employ this cyclic therapy.

DR. GEORGEANNA SEEGAR JONES, BALTIMORE, MD. (By Invitation).—From a purely experimental point of view, Dr. Allen's work is most interesting as it demonstrates what effect progesterone will have on uterine bleeding and opens many theoretical possibilities. In our work we have been more concerned with the practical therapeutic aspects and have approached the problem from a slightly different point of view. First, we have considered only those cases suitable for progesterone therapy where there has been functional uterine bleeding associated with endometrial hyperplasia. We have not considered the term functional uterine bleeding as synonymous endometrial hyperplasia, even in those cases occurring at puberty. Therefore every patient had had a dilatation and curettage before progesterone therapy was instituted in order to establish the diagnosis.

Second, in a study of such cases we have found that a simple dilatation and curettage is all that is necessary to relieve a number of these patients of their symptoms. Therefore, no patient has been treated with progesterone until it has been demonstrated that a therapeutic curettage will not control her bleeding.

Third, we have used a different technique. We have regarded progesterone as a form of substitution therapy and have usually considered it necessary to continue that therapy cyclically over a period of three or four months. That this method is efficacious is demonstrated by the fact that endometrial biopsies taken during the second and third month of treatment have shown an increase in secretory reaction over the first month, when, as a matter of fact, the hyperplastic gland pattern is usually still evident.

In the treatment in 111 cases of endometrial hyperplasia, before we used progesterone, the first three groups, comprising 63 cases, were under the age of 35 and more pertinent to the discussion at hand. Of the 63 cases, 25 responded satisfactorily to a simple dilatation and curettage. In the remaining 38 cases there was a recurrence of abnormal bleeding, and it was necessary to perform more radical procedures in 14 cases. These 38 cases really corresponded to our progesterone-treated cases.

Another series demonstrated the result of treatment with progesterone in 28 cases, all of which had failed to respond to a simple curettage. Only 2 of the series required hysterectomy, one not being treated on our service and the other being operated upon for chronic salpingitis. The remaining 26 cases responded to progesterone. Fourteen are well after a single course of progesterone. Three are still under the initial therapy, and 9 are asymptomatic at present but have had recurrences requiring additional progesterone courses. These 9 cases illustrate Dr. Allen's point, that progesterone therapy will not prevent recurrences of the disease in a certain number of cases.

Another series briefly summarizes the reasons why we feel that progesterone should be at least more adequately tried. Out of 111 cases, treated without the use of hormones, 33 per cent required radical procedures, whereas it has been possible to reduce this figure to 7 per cent with the use of progesterone. It seems that such a reduction is extremely worthwhile since the majority of patients are under 35 years of age.

DR. ALLEN (Closing).—Needless to say, I am well aware of the fact that controls have to be made. In this study detailed observations were made before and after therapy, and an attempt has been made to record as accurately as possible the duration of bleeding in the period just before therapy and in the period just after therapy. With the data arranged in this manner it is permissible to consider the period prior to therapy as a control period. If one were comparing the effects of progesterone with other methods of treatment, such as good food, thyroid and iron, the results obtained in one series with one method of treatment could be compared with the results in another series with another type of treatment. The results obtained are surely not due to chance, for in all instances except two or three, bleeding was measurably less in the month following therapy than in the previous control period.

I believe that in an adolescent girl of 13 or 14, it is a matter of opinion whether it is more radical to use progesterone or to do a diagnostic curettage. I prefer to use progesterone, since it is more rational than curettage, fully as effective, and no more expensive.

We have also observed pain following the progesterone-withdrawal. I might also say that in one patient with amenorrhea we have induced menstrual periods with progesterone. In this patient, two periods were induced by therapy after about fourteen months of amenorrhea. A normal period occurred one month later and then the patient became pregnant.

# TREATMENT OF HYPEREMESIS GRAVIDARUM WITH INTRAMUSCULAR INJECTIONS OF HUSBAND'S BLOOD

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**H**YPEREMESIS gravidarum may vary from a moderately annoying condition to a very serious one in which it becomes imperative to interrupt pregnancy to insure the safety of the mother. Treatment is usually moderately effective, yet the occasional case arises in which the accepted methods of treatment fail. The purpose of this presentation is to present a case which was almost completely relieved of nausea for the first thirty-six weeks of gestation by means of intramuscular injections of the husband's blood, after various other methods of treatment in seven previous pregnancies had failed to control it. The result was striking and no other treatment was instituted or necessary. It is hoped that this report will stimulate further investigations to determine the active factor.

The stimulus for the trial of this method was twofold: (1) The fact that each time after intercourse at night the patient awakened in the morning with a headache similar to that which she experienced from eating certain foods to which she was sensitive, and this fact led to the suspicion that she might be sensitive to all the tissues of her husband. It was thought that the developing tissues of the fetus following the husband's characteristics also might be incompatible with the mother and that the severe hyperemesis might be a response to this tissue incompatibility. The fact that the patient was a universal donor was also suggestive, although this has not been borne out by subsequent cases. It was not beyond the realm of possibility that intramuscular injections of the husband's blood might stimulate the formation of products that would counteract this "tissue sensitivity." (2) The fact that a report from Dr. L. C. Purvis<sup>1</sup> of Westboro, Ontario, in which he stated that he had treated 15 cases of pernicious vomiting of pregnancy with injections of the husband's blood. He used three injections of blood at intervals of three days, the first two being 5 c.c. each and the third being 10 c.c. He said the vomiting ceased in every instance.

## CASE REPORT

The first pregnancy occurred when S. A. H. was 25 years of age. Extreme nausea and vomiting began two weeks after conception and continued unabated despite injections of corpus luteum, intravenous glucose, and calcium until the twenty-eighth week, Feb. 12, 1930, when a vaginal hemorrhage of uterine origin occurred followed by a miscarriage. The prostration was so severe that she was not able to be out of bed during any part of the pregnancy. The premature baby died in three days from multiple hemorrhages. In the mother acidosis was marked, and there was a weight loss of thirty-five pounds, making her weight 110 pounds.



mortality rate of 15.1 per cent. We have excluded these from consideration not only because vaginal cesarean section is virtually an abandoned operation today, but also because the issues involved are different from those of abdominal delivery. We have also excluded eleven extraperitoneal cesarean sections (9 Waters and 2 Latzko) because their number is too small to merit attention. There were no maternal deaths in the extraperitoneal group. Nor have we included cases of rupture of the uterus or instances in which the infant weighed less than 1,500 Gm. in the belief, again, that the problems presented by such cases are different from those of cesarean section as the term is ordinarily used. This leaves 1,333 operations, of which 67.1 per cent were classical, 16.3 per cent low cervical, and 16.6 per cent cesarean section-hysterectomy (Table I). During the past decade the incidence of low cervical section has risen slightly to 20.0 per cent, while that of cesarean section-hysterectomy has fallen by about the same degree to 12.6 per cent.

TABLE I. TYPES OF CESAREAN SECTION

| TYPE                          | CASES | PER CENT |
|-------------------------------|-------|----------|
| Classical                     | 894   | 67.1     |
| Low cervical section          | 218   | 16.3     |
| Cesarean section-hysterectomy | 221   | 16.6     |
|                               | 1,333 | 100.0    |

## INCIDENCE

The period over which the clinic has operated has been divided into four decades, counting backward from Dec. 31, 1941. The experience of the period 1896 to 1901 has been included with that of the first decade since the material of those six years, two cesarean sections, would obviously have no significance if analyzed separately. The incidence has been calculated on the basis of total hospital deliveries (ward and private) in which the infant weighed 1,500 Gm. or more. The incidence is avowedly high (Fig. 1), particularly in the last decade, but in evaluating these figures it is desirable to recall that our clinic admits no normal multiparas to the ward service, handles a clientele which is 50 per cent negro, and during the past six years has served as the referral center for all pathologic cases encountered in the State Board of Health's nineteen prenatal clinics scattered throughout the counties of Maryland. The marked increase in our incidence of cesarean section in the last decade is due chiefly to the institution of this referral service, but partly to a more liberal use of abdominal delivery in certain cases of placenta previa, fulminating pre-eclampsia, and in certain patients who have had previous cesarean sections.

## INDICATIONS

As may be seen in Table II, the indications fall into six groups as follows: contracted pelvis and mechanical dystocia, 58.4 per cent; toxemias, 15.0 per cent; previous cesarean section, 11.2 per cent; hemorrhage, 6.6 per cent; intercurrent disease, 3.0 per cent; and unclassified, 5.8 per cent. In the first group, contracted pelvis naturally accounts for the great majority of the cases, constituting the primary indication in 44.5 per cent of the whole series. Uterine inertia is the second most common cause in this group, prompting 5.4 per cent of the operations. This heading includes, along with uterine inertia, cases of so-called

# THE EXPERIENCE OF THE JOHNS HOPKINS HOSPITAL WITH CESAREAN SECTION\*

AN ANALYSIS OF 1,333 OPERATIONS

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IN VIEW of the many statistical studies of cesarean section already published, some explanation would seem necessary in venturing to present yet another. The present group of cases appears worthy of record for a number of reasons. In the first place, it is one of the largest series thus far reported, comprising 1,333 operations, and therefore permits of statistical analysis with a minimum of sampling error. Second, 718 of these cesarean sections were performed because of contracted pelvis. These 718 cases of contracted pelvis necessitating abdominal delivery occurred in a total series of 7,226 cases of pelvic contraction. Quite apart from the size of this group of contracted pelvises, and more important, is the fact that the late Dr. Whitridge Williams, from the earliest days of the clinic, insisted on meticulous pelvic mensuration, including a diagonal conjugate measurement, checked by a senior staff member. Almost half of the total operations here reported, or 43.7 per cent, were done under his surveillance. His conservatism in the use of cesarean section in contracted pelvis and his rigid adherence to contraindications are well known; and his successors have endeavored in general to follow the same policy. We, however, have had the advantage of a technical aid during the past decade which was unknown throughout the greater part of his time, namely x-ray pelvimetry, and, as we shall show, this adjunct has played an important role in the recent management of these cases and in the results achieved. We have here then a large series of contracted pelvises, accurately measured, many by x-ray, and managed, we believe, in accordance with a fairly uniform and conservative policy. This affords unusual opportunity for studying the prognosis of labor in various degrees of pelvic contraction. Third, the series includes 894 classical cesarean sections performed by more than fifty operators over a span of forty-five years and is thus large and variegated enough to permit of certain conclusions about the possibilities and limitations of that operation.

## TYPES OF OPERATION

In the early years of the service thirty-three vaginal cesarean sections were done, mostly for eclampsia. There were five maternal deaths, a

\*Read, by Dr. Eastman, at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.

or 9.9 per cent, were handled by abdominal delivery. During the first three decades, the incidence rose progressively to 13.8 per cent, but has fallen to 10.4 per cent in the last ten years (Fig. 2). Fig. 3 shows our incidence of cesarean section in cases of contracted pelvis according to decade and diagonal conjugate measurement. For example, among patients with diagonal conjugates between 9.0 and 9.4, only 60 per cent

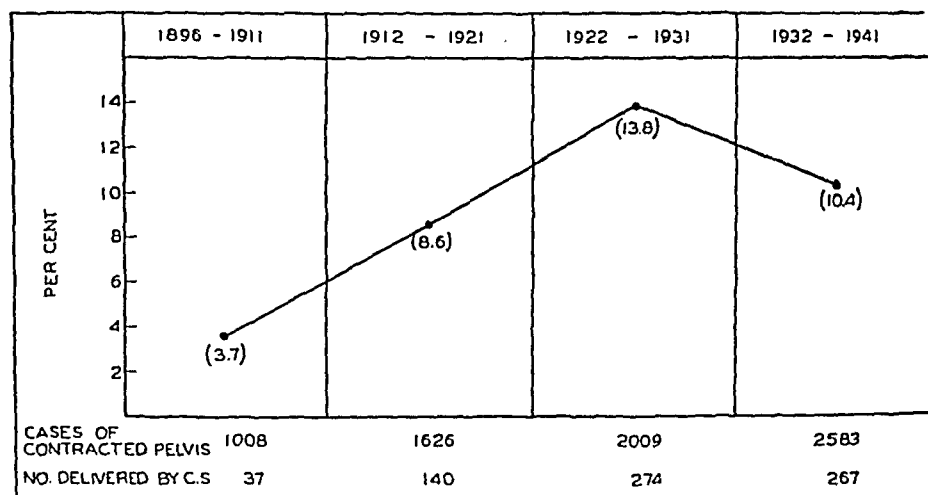


Fig. 2.—Showing incidence of cesarean section in cases of contracted pelvis (c.d. of 11.5 cm. or less) by decades. Total cases of contracted pelvis, 7,226; number delivered by cesarean section, 718; percentage delivered by cesarean section, 9.9.

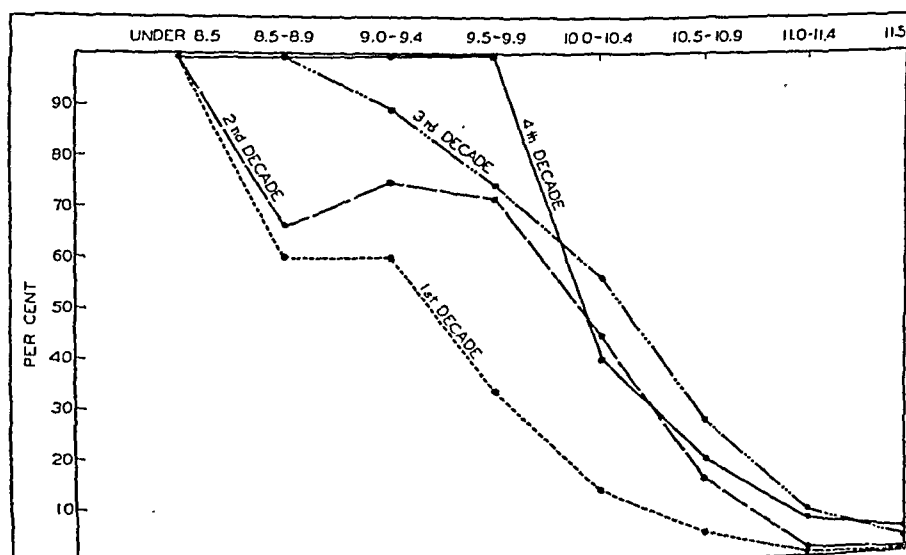


Fig. 3.—Showing incidence of cesarean section in cases of contracted pelvis according to decade and diagonal conjugate measurement.

were delivered abdominally in the first decade, 75 per cent in the second, 87.5 per cent in the third, but in the fourth ten-year period, 100 per cent. Indeed, during the past decade all women with diagonal conjugates under 10.0 have been delivered abdominally. On the other hand, in the group between 10.0 and 10.9, a substantial reduction in the incidence of cesarean section has occurred during the past decade, the percentage of abdominal deliveries being definitely less than in the last decade and in the case of the 10.0 to 10.4 group, being even lower

cervical dystocia, dystocia dystrophy syndrome, and prolonged labor with bad obstetric history. The term "disproportion" is not listed as a single cause since, in our experience, it is always secondary to some specific cause such as contracted pelvis, over-size baby, malpresentation, or some combination of such specific causes. In the series as a whole, fulminating pre-eclampsia accounts for 7.7 per cent of the operations, but in the last decade for 12.7 per cent, a sharp increase which will be discussed subsequently.

While it is customary to report incidence and indications in the manner we have done, a more accurate picture of the policy of a given clinic toward cesarean section may be had by reporting the percentage of cases in any specified complication which are treated by cesarean section. For instance, among our 7,226 cases of contracted pelvis, 718,

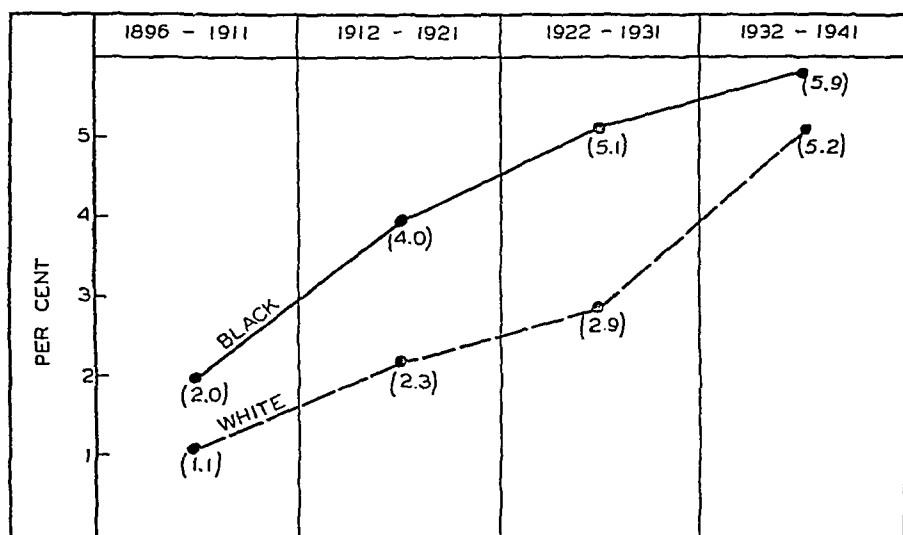


Fig. 1.—Showing the increasing incidence of cesarean section by decades and race.

TABLE II. PRIMARY INDICATIONS

|                           |   | CASES | %    |
|---------------------------|---|-------|------|
| Contracted Pelvis         | Contracted Pelvis                         | 595   | 44.5 |
| and                       | Uterine inertia                           | 72    | 5.4  |
| Mechanical Dystocia:      | Malpresentations (45); Oversize baby (14) | 59    | 4.4  |
|                           | Tumor blocking birth canal                | 21    | 1.5  |
|                           | Elderly primigravidas                     | 35    | 2.6  |
| 58.4%                     | Total for group                           | 781   | 58.4 |
| Toxemias:                 | Pre-eclampsia                             | 104   | 7.7  |
|                           | Hypertensive vascular disease             | 93    | 6.9  |
|                           | Eclampsia (before 1920)                   | 6     | 0.4  |
| 15.0%                     | Total for group                           | 203   | 15.0 |
| Previous Cesarean Section | Previous cesarean section                 | 115   | 11.2 |
| 11.2%                     | Total for group                           | 115   |      |
| Hemorrhage:               | Placenta previa                           | 40    | 3.0  |
|                           | Premature separation of placenta          | 48    | 3.6  |
| 6.6%                      | Total for group                           | 88    | 6.6  |
| Intercurrent Disease:     | Heart disease, tuberculosis, etc.         | 40    | 3.0  |
| 3.0%                      | Total for group                           | 40    |      |
| Unclassified:             | Sterilization (before 1930), 34; Other 72 | 106   | 5.8  |
| 5.8%                      | Total for group                           | 106   |      |

third factor which has proved helpful in our hands in establishing the prognosis of labor in contracted pelvis is the behavior of the cervix. Stated briefly, in degrees of contracted pelvis incompatible with delivery from below, the cervix rarely dilates satisfactorily. By way of supporting this statement we have studied forty-nine labors in women with contracted pelvis in which cesarean section was finally performed after thirty or more hours of labor and found that the cervix had reached full dilatation in only eight of these cases, or less than one-sixth; in twenty-nine of the cases, or one-half, the dilatation was less than 5 cm.; in thirteen or one-fourth, it was less than 3 cm. even after thirty hours. To be sure, some of these cases may have been associated with uterine inertia, but the clinical fact remains that tests of labor which ultimately fail are usually stigmatized from the very beginning by a cervix which does not dilate; and conversely, among those which are ultimately successful, the cervix is usually near complete dilatation after twelve hours.

Turning now to pre-eclampsia, the percentage of cases of that complication treated by cesarean section has risen from 2.0 per cent in the first three decades to 7.8 per cent in the last ten-year period. In other words, during the recent period about one pre-eclamptic in every thirteen is delivered by the abdominal route. With occasional exceptions, all of the pre-eclampsies so delivered fulfilled the following criteria: the disease appeared fulminating with convulsions imminent and did not respond to medicinal treatment; the pregnancy was four or more weeks from the expected date of confinement and conditions were unfavorable for rupture of the membranes, that is, the head was high and the cervix long, hard and closed. We believe that cesarean section is indicated under such circumstances. The reason for this attitude is not so much the fear of convulsions as the fact that the long period of time necessary to carry such patients before vaginal delivery can be effected safely, imposes a greater risk in the way of permanent vascular damage, than is represented by the general risk of cesarean section.

Our incidence of cesarean section in other common complications is as follows: previous cesarean section (no other indication), 53.4 per cent for the series as a whole, 63.6 per cent for the past decade; placenta previa, 20.8 per cent for the series as a whole, 38.0 per cent for the past decade; premature separation of the placenta, 27.3 per cent for the series as a whole, 31.0 per cent for the past decade; elderly primigravidas, 18.6 per cent for the series as a whole, 25.0 per cent for the past decade.

TABLE III. MATERNAL MORTALITY ACCORDING TO DECADE AND TYPE

|                                   |           |   |      |
|-----------------------------------|-----------|---|------|
| 1333 Operations                   | 38 Deaths | Total mortality                         | 2.8% |
| 894 Classical                     | 20 Deaths | Classical mortality                     | 2.2% |
| 218 Low Cervical Section          | 6 Deaths  | Low cervical section mortality          | 2.7% |
| 221 Cesarean section-hysterectomy | 11 Deaths | Cesarean section-hysterectomy mortality | 5.0% |

| TYPE OF OPERATION             | 1896-1911 |        |      | 1912-1921 |        |     | 1922-1931 |        |      | 1932-1941 |        |     |
|-------------------------------|-----------|--------|------|-----------|--------|-----|-----------|--------|------|-----------|--------|-----|
|                               | CASES     | DEATHS | %    | CASES     | DEATHS | %   | CASES     | DEATHS | %    | CASES     | DEATHS | %   |
| Classical                     | 24        | 4      | 16.6 | 113       | 2      | 1.8 | 244       | 6      | 2.4  | 513       | 8      | 1.5 |
| Low cervical section          | 0         | 0      | 0    | 0         | 0      | 0   | 66        | 3      | 4.5  | 152       | 3      | 2.0 |
| Cesarean section-hysterectomy | 17        | 1      | 5.8  | 43        | 1      | 2.3 | 76        | 8      | 10.5 | 85        | 2      | 2.2 |

than in the second decade. It is this diminished incidence of cesarean section in the 10.0 to 10.9 group which has brought about the lowering in the total incidence of cesarean section in contracted pelvis as shown in Fig. 2.

Fig. 4 shows that despite the diminished incidence of cesarean section in contracted pelvis during the past decade, a dramatic reduction has occurred in our stillbirth and neonatal mortality among this group. All mortality figures reported are uncorrected. In the white, the figure has fallen to one-third that of the previous decade and in the black to one-half. We believe that there are three main factors responsible for these results. (1) X-ray pelvimetry has made possible a more precise

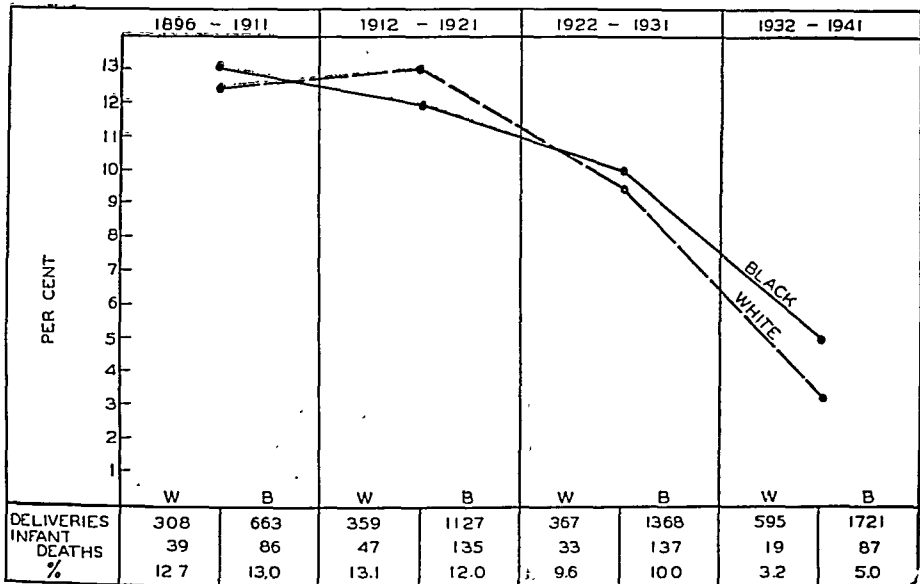


Fig. 4.—Showing the stillbirth and neonatal mortality rate by decade in cases of contracted pelvis delivered vaginally (6,508 deliveries).

estimation of pelvic size and architecture in the troublesome group with diagonal conjugates between 10.0 and 11.0 and has permitted a more correct prognosis in regard to the possibilities of pelvic delivery. Diagonal conjugate measurements above 11.5 almost always rule out contractions of the inlet, but measurements between 10.0 and 11.0 may reflect imperfectly the true or obstetric conjugate diameter. Thus, among women with diagonal conjugates of 10.5 cm., the obstetric conjugate may vary between 8.2 and 10.3, a range of more than two centimeters. X-ray study of the architecture of the midpelvis also affords valuable information as to which cases may be delivered vaginally and which demand cesarean section. In our experience, then, this technical adjunct has played an important role not only in reducing infant mortality in the contracted pelvis group but in eliminating unnecessary cesarean section among these patients. (2) Another factor which may be credited with the results shown in Fig. 3 is the realization that tests of labor in patients with contracted pelvis, when carried beyond thirty hours, yield a fetal mortality rate in excess of 30 per cent, as shown some years ago in our clinic by Peckham and Kuder. With rare exceptions a careful weighing of all the factors concerned, including x-ray findings, after twelve hours of labor, is adequate to yield a proper decision as to whether or not abdominal delivery is necessary. (3) A

During recent years a number of clinics have reported a reduction in their maternal mortality rates in cesarean section and have attributed this to abandoning the classical operation in favor of the low cervical technique. From the viewpoint of straight thinking it is worth while noting that our maternal mortality with classical cesarean section in

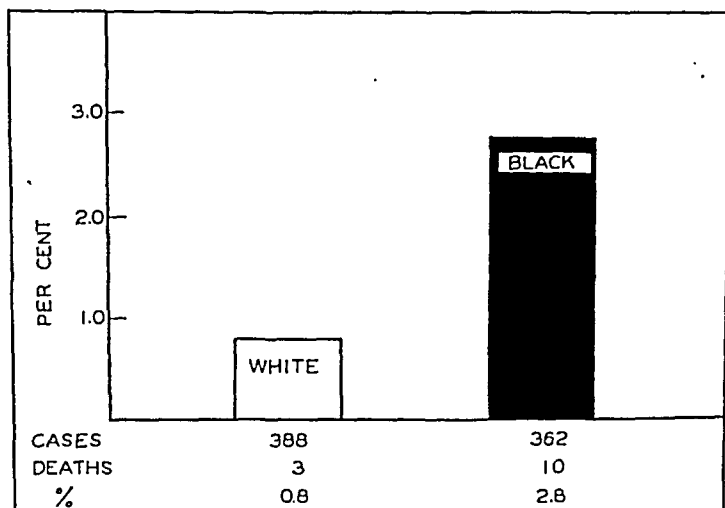


Fig. 6.—Showing the maternal mortality in the last decade according to race.

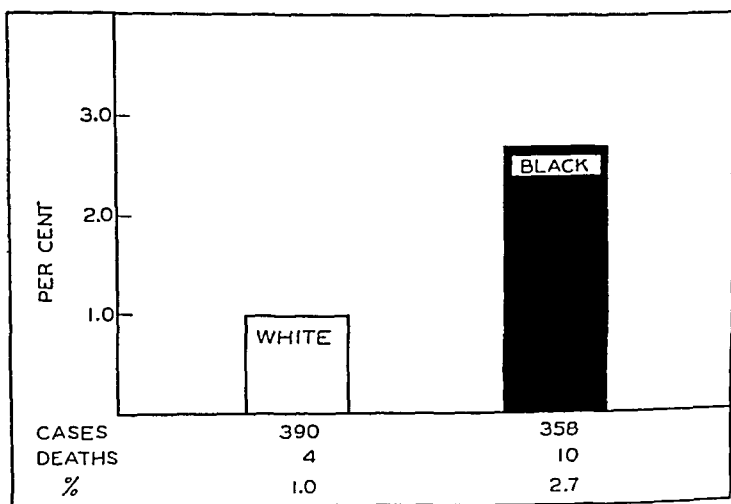


Fig. 7.—Showing the maternal mortality in elective cesarean section according to race.

white women, counting from 1896, was 1.1 per cent in 354 elective cases; in the last decade it was 0.7 per cent in 275 similar cases; no patients died from peritonitis, as attested by autopsy. We believe, accordingly, that prior to the onset of labor, classical cesarean section will give as good immediate results as low cervical provided that contraindications are rigidly observed. Hence, we suspect that the improved mortality rates which have been credited to the low cervical technique are in many instances the result of stricter observance of contraindications, better judgment in the selection of cases and more blood transfusions. So far

## MATERNAL MORTALITY

As shown in Table III, among the 1,333 operations extending back to 1896, there were 38 deaths, a gross uncorrected mortality rate of 2.8 per cent. Among the 894 classical operations, there were 20 deaths, a rate of 2.2 per cent. The respective mortality rates for low cervical section and cesarean section hysterectomy were 2.7 and 5.0 per cent. During the past decade there were 513 classical cesarean sections with 8 maternal deaths, a mortality rate of 1.5 per cent. The opinion has been expressed that any death rate above 1 per cent in cesarean section is too high; and we are in accord with this view so far as the white race is concerned, but doubt if it can be approached in the black. As shown in Fig. 5, the total maternal mortality for the white race was 2.0 per cent and for the black, 3.5 per cent. During the past decade the corresponding percentages were 0.8 and 2.8, respectively (Fig. 6.). That this difference is not due to a preponderance of neglected cases of labor in the black race is shown by Fig. 7. Here it will be seen that even in elective cases the mortality of the colored race is two and one-half times that of the white.

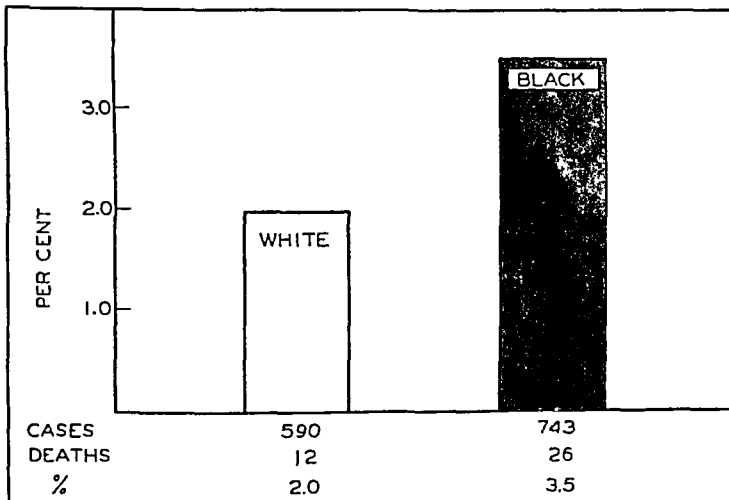


Fig. 5.—Showing the maternal mortality in the total series according to race.

*Causes of Maternal Deaths.*—The causes of the 38 maternal deaths are shown in Table IV. The most common cause was shock and hemorrhage. A critical analysis of these 9 cases would suggest, on hindsight, that the following errors of commission and omission played important roles in these fatalities: (1) The imposition of a shocking operation (cesarean section, hysterectomy in 5 of the 9) on patients already shocked from premature separation of the placenta, or exhausted by prolonged labor; (2) failure to protect such patients against shock by the liberal use of blood transfusions before, during, and after these operations. Less than one-fourth of the deaths (6 of the 38) were due to generalized peritonitis, but an equal number were the result of paralytic ileus alone, as attested by autopsy. In this latter group the earlier and more persistent use of continuous gastric suction might have saved some of these women. Of the 4 anesthetic deaths, 3 occurred in women who had been in labor over thirty hours, a circumstance attesting the fact that patients exhausted by long labors are poor anesthetic risks as well as poor risks from the viewpoint of shock.



hours of ruptured membranes or twenty-four hours of labor. This has not resulted in an increase of cesarean section notwithstanding this rule.

In the first series of 1,000 cases the morbidity was 43.8 per cent. In the second series the morbidity was 32.9 per cent, a decrease of nearly 11 per cent. In the first series there was a mortality of 8 cases, or 0.8 per cent; in the second series a mortality of 2 cases, or 0.4 per cent, a decrease of 50 per cent in our mortality. And I might say that 50 per cent of the mortality in the first series was associated with infection, whereas in the second series there was no mortality from infection. It is very important then to recognize the contraindications against cesarean section, especially from the standpoint of the possibility of an infection which may terminate fatally.

Another point I think is extremely important which Dr. Eastman did not mention is the question of outlet contraction. It is important to recognize it early as it is a bar frequently to natural or instrumental delivery. If it is not diagnosed early the contraindications for cesarean section have arisen before it is recognized and, of course, then the operation is too late to be advantageous.

Another point is that there is a cumulative risk from cesarean section. A woman who has an initial cesarean section is exposed to the risk of a second operation. In the morbidity series we found that 25.6 per cent of approximately 197 cases had had one previous cesarean section, and that 6.7 per cent had had more than one cesarean section.

The lower segment operation was done in 87.2 per cent of the morbidity cases; the classical operation in only 0.6 per cent. Hysterectomy was associated with cesarean section in 10.3 per cent, and the vaginal operation was done in 1.8 per cent, which corresponds rather closely with the figures given by Dr. Eastman. We did a sterilization operation in 42 per cent of the morbidity cases.

The indications for cesarean section were hemorrhage in 11.5 per cent; toxemia in 19.5 per cent; a cardiac condition in 5.5 per cent; previous cesarean section in 6.7 per cent; coexistent pathology in 4.2 per cent; disproportion and dystocia in 52.5 per cent.

Local anesthesia was used exclusively in 53 per cent; combined with general anesthesia in 20.9 per cent; and general anesthesia alone in 26 per cent. These figures apply to the morbidity series and not to the entire series of cases.

DR. HARVEY B. MATTHEWS, BROOKLYN, N. Y.—No discourse on cesarean section should omit a consideration of fetal mortality. At the Methodist Hospital of Brooklyn, from April 1, 1924, to Aug. 1, 1941, there were a total of 31,242 deliveries with a total of 2,089 fetal deaths or a rate of 6.6 per cent. In this series there were 1,116 cesarean sections with a total of 68 fetal deaths, giving a rate of 6 per cent. I appreciate the fact that there were considerable more vaginal deliveries than deliveries by cesarean section; however, the figures do bring out the point that fetal survival is not necessarily simply a matter of performing cesarean section.

Let us take, for the sake of comparison, the fetal mortality rate in cesarean section in 3 other representative hospitals. We find the following: The Chicago Lying-in, 6.7 per cent in 1,000 cesarean sections; The Woman's Hospital, New York, 6.69 per cent in 912 cesarean sections; The Philadelphia Lying-in, 10.8 per cent in 830 cesarean sections. Our rate of 6.0 per cent in 1,116 sections compares favorably with these figures.

In our series, prematurity constituted the largest group of nonsurvivals (25, or 4.0 per cent) and this is in line with other reports. Cesarean section apparently gives no better assurance of survival of the viable premature than well-managed vaginal delivery. Congenital anomalies made up the next largest group in our

TABLE IV. CAUSES OF 38 MATERNAL DEATHS IN 1,333 CESAREAN SECTIONS  
(MORTALITY 2.8%)

| <i>Deaths Due Directly to Operation</i>  |   |                               |   |
|--|---|-------------------------------|---|
| 1. Shock and hemorrhage  | 9 | Classical                     | 4 |
|  |   | Cesarean section-hysterectomy | 5 |
| 2. Generalized peritonitis   | 6 | Classical                     | 4 |
|  |   | Cesarean section-hysterectomy | 1 |
|  |   | Low cesarean section          | 1 |
| 3. Ileus alone. (No general peritonitis;<br>no mechanical obstruction)                           | 6 | Classical                     | 3 |
|  |   | Cesarean section-hysterectomy | 1 |
|  |   | Low cesarean section          | 2 |
| 4. Ileus due to mechanical obstruction   | 3 | Classical                     | 3 |
| 5. Thrombophlebitis with septicemia  | 4 | Classical                     | 2 |
|  |   | Cesarean section-hysterectomy | 1 |
|  |   | Low cesarean section          | 1 |
| 6. Anesthesia (including one aspiration<br>pneumonia with death on first post-<br>operative day) | 4 |                               |   |
|  |   | 32                            |   |
| <i>Deaths Due to Intercurrent Disease</i>  |   |                               |   |
| Hypertensive vascular disease  |   |                               | 2 |
| Acute thromboendocarditis  |   |                               | 1 |
| Cerebral hemorrhage in pre-eclampsia   |   |                               | 1 |
| Primary meningitis   |   |                               | 1 |
| Miliary tuberculosis   |   |                               | 1 |
|  |   |                               | 6 |

as the late results are concerned, that is, the integrity of the scar, an inquiry into the literature shows a woeful lack of statistically valid, factual information supporting the supposed superiority of the low segment scar.

The odds in the present series are weighted heavily against low cervical cesarean section inasmuch as this operation, until very recent years, has been reserved for potentially infected cases and any attempt to compare these cases statistically with our classical series would not be equitable. Nevertheless, our experience suggests that even this procedure becomes increasingly hazardous after eighteen hours of labor and in such cases had best be superseded either by cesarean section-hysterectomy or an extraperitoneal operation.

#### DISCUSSION

DR. FRED L. ADAIR, CHICAGO, ILL.—There are two, possibly three, major differences between the series at the Chicago Lying-In Hospital and the series at the Johns Hopkins Hospital. In the first place, our series is limited to the white race. Second, our series is based predominantly on the low cervical operation, and, third, although it was not mentioned in the paper, I believe that our percentage of cases done under local anesthesia is much higher than in Dr. Eastman's clinic.

We have reported 1,000 cesarean sections covering a period from 1931 to 1938 in 18,009 deliveries, an incidence of 5.5 per cent. From March 1, 1938, to March 1, 1942, there were 11,232 deliveries with 497 cesarean sections, an incidence of 4.4 per cent. I would like to point out that during this latter period we have insisted more vigorously on reaching a decision for or against cesarean section after twelve

Second pregnancy occurred eight months later, October, 1930. After two weeks, nausea and vomiting became severe and at the end of six weeks the pregnancy was terminated by a curettage. As in the previous and subsequent pregnancies, vomitus consisted of almost pure bile and nothing taken by mouth could be retained. Corpus luteum, intravenous glucose and calcium were given during the pregnancy with little effect.

On Feb. 25, 1933, a myomectomy for fibroma of the uterine wall was performed because of irregular menses and metrorrhagia. It was about the size of a small grapefruit.

Third pregnancy was accompanied by the same extreme nausea and vomiting of lemon-colored fluid. A spontaneous miscarriage took place at the twenty-fourth week, Dec. 27, 1935. The weight loss was moderate and nothing was retained by mouth unless lobster was taken during the meal. Thyroid was given during this pregnancy and also proluton with little effect on the nausea.

Fourth pregnancy was similarly accompanied by extreme nausea and vomiting with prostration, and ended at the fourth month (April 14, 1936) in spontaneous miscarriage.

Fifth pregnancy followed a similar stormy course, ending on Dec. 24, 1936, at eleven weeks in spontaneous abortion.

Sixth pregnancy: Extreme nausea and vomiting began at the second week as in previous pregnancies. During this pregnancy proluton was given and also insulin twenty minutes before the evening meal. Atropine sulfate was also given by mouth. As with other pregnancies the patient was constantly confined to bed, being able to retain some evening meals, but never anything before 2 P.M. except white radishes, which were found to reduce the nausea considerably. Weight loss was less, but at the twenty-fourth week spontaneous miscarriage took place, July, 1938. Moderate doses of wheat germ oil, 30 drops, twice daily, and wheat germ, one tablespoon, twice daily, were given during this pregnancy. The wheat germ was tolerated better than the oil, which increased the nausea.

Seventh pregnancy: Vomiting began at the fourth week and was extreme. A few evening meals in which lobster was included were retained. Proluton,  $\frac{1}{8}$  mg., was given intramuscularly daily from the second to the fifth month and twice weekly subsequently. The severe vomiting continued until a spontaneous miscarriage took place at the twenty-eighth week, June 18, 1939.

In each of the preceding seven pregnancies, the vomiting began during the first month and was extreme with moderate to considerable weight loss with only an occasional evening meal retained. The vomitus consisted for the most part of clear lemon-colored bile. Sometimes food was retained for several hours, there being apparently a lack of gastric peristalsis with a spastic condition of the pylorus which later was confirmed by fluoroscopic examination. Food taken late one day would often be brought up the next morning.

In the eighth pregnancy, however, there was a complete change, due, apparently, to a different method of treatment.

Injections of 2 c.c. of the husband's blood were given intramuscularly at intervals of from two to fourteen days, throughout the pregnancy.

This method of treatment was further suggested by the incompatible blood grouping of husband and wife in the present instance, since the

series of nonsurvivals (12 or 1.9 per cent), and here I should like to point out that, whenever possible, every cesarean section should be preceded by an x-ray examination of the fetus in utero and thus rule out, at least, certain types of anomalies. Neonatal infection, eclampsia, hemorrhagic disease of newborn, and intracranial hemorrhage were among other causes listed.

In conclusion, I should like to emphasize again that cesarean section carries with it a sizable fetal mortality and that we should constantly reiterate this fact in all our discussions of cesarean section to the end that the lay public, as well as the medical profession, may more fully realize that abdominal section is "no positive assurance of a live baby."

DR. WILLIAM R. NICHOLSON, PHILADELPHIA, PA.—The anesthesia is an important consideration in determining the fetal mortality in cesarean section. For some time I have made a practice of having the woman brought into the operating room, placed on the table, catheterized, and the abdomen prepared before any anesthetic is given. A very slight anesthesia, not much deeper than the first stage, is given and as soon as the woman is unconscious the incision is made. The baby is probably only two minutes under very moderate anesthesia before its delivery. This has made a tremendous difference. Formerly I did not do a cesarean section unless I had a man on the other side of the table perfectly competent to take over the patient, thus enabling me to attend to the resuscitation of the baby. Under this plan of reduced amount of anesthesia for the baby in utero we find that the baby inspires as soon as delivered.

DR. EASTMAN (Closing).—Since the subject of cesarean section runs almost the whole gamut of obstetrics, it was obviously impossible to deal with more than a few aspects of the problem in this survey. With regard to Dr. Adair's comments upon outlet contraction, our experience has been that outlet contraction *alone* is rarely an indication for abdominal delivery. In a primigravida with a breech presentation and outlet contraction, or in a woman with a large baby and outlet contraction, it may occasionally be necessary, but in our series there are only 12 instances in which cesarean section was performed solely on the grounds of a diminished bi-ischial diameter.

In regard to our fetal mortality, this figure was 6.0 per cent for the entire series. The greater number of these stillbirths and neonatal deaths were the result of premature separation of the placenta, placenta previa, and toxemias of pregnancy.

## THE POSSIBLE ETIOLOGIC ROLE OF GYNECOLOGIC LESIONS IN THE PRODUCTION OF HYPERTENSION\*

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THAT arterial hypertension is frequently associated with renal disease has been accepted as a fact since the classic contributions of Bright. The recent brilliant experimental work of Goldblatt, Paged, and others, however, has led to a renewed interest in this subject which has resulted in the recording of much careful investigation, both experimental and clinical. The recent literature is so replete with articles, many of which contain complete bibliographies, that a comprehensive review would be not only time-consuming but superfluous.

Since the observations to be recorded herewith are at least suggestive that hypertension may result from partial ureteral occlusion, a brief review of the literature of this phase of the subject is appropriate.

From the field of animal experimentation the reports are meager and conflicting. Hinman and Morrison's<sup>1</sup> work with experimental hydronephrosis in rabbits led them to suspect that renal blood flow was diminished. Enger, Gerstner and Sarre<sup>2</sup> using direct measurements found that when the intraureteral pressure was over 60 there was a significant fall in renal blood flow, often as much as 35 per cent. Levy, Mason, Harrison and Blalock<sup>3</sup> measured renal blood flow after ureteral occlusion in eight dogs; the average reduction was 41 per cent. Three of their dogs developed hypertension, and Megibow, Friedberg, Rodbard and Katz<sup>4</sup> reported hypertension in 6 of 7 dogs after bilateral complete ureteral occlusion, and in 5 of 7 dogs after partial occlusion of both ureters. These workers have explained the frequent occurrence of hypertension in their animals on the basis of renal ischemia. Eichelberger<sup>5</sup> on the contrary was unable to demonstrate the development of hypertension in any of 20 dogs subjected to partial ureteral constriction, even though half of her dogs progressed into uremia.

On the clinical side Schroeder and Steele<sup>6</sup> have observed bilateral hydronephrosis in 11 and unilateral hydronephrosis in 20 of 71 patients with essential hypertension. Approaching the subject from the opposite angle, Braasch, Walters and Hammer<sup>7</sup> found hypertension in only 72, or 22 per cent, of 372 patients with hydronephrosis; but in 10, or 34.4 per cent, of 29 patients in whom the hydronephrotic kidney was removed, or the hydronephrosis corrected by conservative surgical measures, the blood pressure returned to normal and remained so for from one to five years following operation. Such observations can only lead to the conclusion that hydronephrosis due to ureteral obstruction

\*Read at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.

must in some individuals at least result in arterial hypertension. The failure of every individual so to respond to the presence of hydro-nephrosis merely falls in line with similar observations regarding many types of renal disease. Even the severest forms of atrophic pyelonephritis with marked sclerosis of the arterioles and small arteries of the kidney, the type of lesion most commonly considered as playing a large etiologic role in the production of hypertension, may at times occur in individuals with perfectly normal blood pressures. This fact has been well demonstrated recently by Crabtree and Chaset<sup>8</sup> as well as others. To explain the lack of uniformity of response in arterial tension to similar renal lesions on the part of different individuals is difficult and beyond the scope of this paper.

The observations to be recorded herein were begun more or less accidentally. About three years ago one of us (Everett), with the collaboration of W. J. Sturgis,<sup>9</sup> decided to study the effect of a variety of major gynecologic disorders upon the urinary tracts. In undertaking this study we hoped to be able to observe personally findings recorded previously in the case of large pelvic tumors such as uterine fibroids and ovarian cysts by Kretschmer and Kanter,<sup>10</sup> and in the case of uterine prolapse by Brettauer and Rubin<sup>11</sup> and by Wallingford.<sup>12</sup> In addition, we wished to make similar observations on patients suffering from pelvic inflammatory disease, a phase of the subject concerning which practically nothing could be found in the literature. Exactly 50 per cent of

TABLE I. URINARY TRACT DISORDERS OBSERVED BEFORE THE INSTITUTION OF TREATMENT IN 100 PATIENTS WITH VARIOUS GYNECOLOGIC LESIONS:

A—UPPER TRACT DILATATION

| TYPE OF LESION                                  | NO.<br>STUDIED | BILATERAL DILATATION |      | UNILATERAL DILATATION |      |
|---|----------------|----------------------|------|-----------------------|------|
|   |                | NO.                  | %    | NO.                   | %    |
| 1. Uterine fibroids                             |                |                      |      |                       |      |
| a. Above pelvic brim with salpingitis           | 13             | 8                    | 61.5 | 2                     | 15.4 |
| b. Above pelvic brim without salpingitis        | 17             | 6                    | 35.3 | 4                     | 23.5 |
| c. Below pelvic brim with salpingitis           | 8              | 1                    | 12.5 | 1                     | 12.5 |
| d. Below pelvic brim without salpingitis        | 9              | 1                    | 11.1 | 2                     | 22.2 |
| 2. Chronic salpingitis                          | 9              | 1                    | 11.1 | 3                     | 33.3 |
| 3. Subacute salpingitis with pelvic masses      | 12             | 4                    | 33.3 | 3                     | 25.0 |
| 4. Pelvic abscess                               | 7              | 2                    | 28.6 | 2                     | 28.6 |
| 5. Ovarian cyst                                 | 4 + 1*         | 1 + 1*               | 40.0 |                       |      |
| 6. Carcinoma of ovary                           | 5              | 3                    | 60.0 |                       |      |
| 7. Complete procidentia of uterus               | 3 + 1*         | 1                    | 25.0 | 1                     | 25.0 |
| 8. Incomplete prolapse of uterus with cystocele | 10             | 3                    | 30.0 | 1                     | 10.0 |
| 9. Cystocele without prolapse of uterus         | 3              | 0                    | 0    | 0                     | 0    |
| Total   | 100            | 31                   | 31.0 | 19                    | 19.0 |

\*Cases also included in one of the groups with uterine fibroids.

our subjects showed some degree of either bilateral or unilateral pelvic and ureteral dilatation. The distribution of such dilatation among various gynecologic diagnostic groups is shown in Table I, and the results of observation of urinary tract abnormalities other than dilatation is shown in Table II. From Table II it can also be seen that 36 per cent of the 100 patients were found to have some degree of arterial hypertension. This seemed an extraordinarily high incidence of this condition for a group of patients whose average age was only 37.06 years, and of whom only 14 were more than fifty years of age. Further analysis revealed that 25 of the patients with hypertension were in the group of 50 showing pelvic and ureteral dilatation, an incidence of 50 per cent for this group, while only 11 or 22 per cent, of those without upper urinary tract dilatation were hypertensive.

TABLE II. OBSERVATION ON THE URINARY TRACTS OTHER THAN THE PRESENCE OR ABSENCE OF UPPER TRACT DILATATION IN 100 GYNECOLOGIC PATIENTS

| TYPE OF CONDITION                            | NO. STUDIED | BLADDER INFECTION |      | UPPER TRACT INFECTION |      | DIMINISHED FUNCTION |      | HYPERTENSION |      |
|--|-------------|-------------------|------|-----------------------|------|---------------------|------|--------------|------|
|  |             | NO.               | %    | NO.                   | %    | NO.                 | %    | NO.          | %    |
| Uterine fibroids without pelvic inflammation | 26          | 8                 | 30.8 | 4                     | 15.4 | 3                   | 11.5 | 12           | 46.1 |
| Uterine fibroids with pelvic inflammation    | 21          | 6                 | 28.6 | 1                     | 4.8  | 3                   | 14.3 | 9            | 42.8 |
| Pelvic inflammation without fibroids         | 28          | 5                 | 18.0 | 1                     | 3.6  | 3                   | 10.7 | 5            | 18.0 |
| Other conditions                             | 25          | 6                 | 24.0 | 1                     | 4.0  | 1                   | 4.0  | 10           | 40.0 |
| Total  | 100         | 23                | 23.0 | 7                     | 7.0  | 10                  | 10.0 | 36           | 36   |

Of the 23 bladder infections 11 were in the group without upper tract dilatation and 12 in that with dilatation.

Of the 7 upper tract infections only 1 was in the group without dilatation.

None of the 10 cases with diminished function were in the group without dilatation.

Of the 36 hypertensive patients 11 were among the 50 patients without dilatation, an incidence of 22 per cent for the group, and 25 were in the group with dilatation, or an incidence of 50 per cent for this group.

Average age of the 100 patients: 37.06 years. Only 14 were more than 50 years of age.

Following these observations it was decided to continue the studies upon as many of these 100 patients as possible in order to observe the effects of appropriate gynecologic treatment upon the dilated urinary tracts and upon the hypertension. For the purpose of these studies the 100 patients were divided into 4 groups as follows:

Group I, 39 patients with neither urinary tract dilatation nor hypertension.

Group II, 25 patients with both urinary tract dilatation and hypertension.

Group III, 25 patients with urinary tract dilatation without hypertension.

Group IV, 11 patients with hypertension without urinary tract dilatation.

**TABLE III. OBSERVATION ON THE UPPER URINARY TRACTS FOLLOWING APPROPRIATE GYNECOLOGIC TREATMENT IN 30 OF THE 50 PATIENTS SHOWING UPPER TRACT DILATATION BEFORE TREATMENT**

| TYPE OF CONDITION   | NO.<br>FOLLOWED | RETURNED TO<br>NORMAL |      | PARTIAL<br>REGRESSION |       | NO CHANGE |      |
|---|-----------------|-----------------------|------|-----------------------|-------|-----------|------|
|   |                 | NO.                   | %    | NO.                   | %     | NO.       | %    |
| Uterine fibroids without pelvic inflammation                      | 8               | 5                     | 62.5 | 1                     | 12.5  | 2         | 25.0 |
| Uterine fibroids with pelvic inflammation                         | 8               | 4                     | 50.0 | 2                     | 25.0  | 2         | 25.0 |
| Pelvic inflammatory disease, chronic, subacute and pelvic abscess | 10              | 3                     | 30.0 | 5                     | 50.0  | 2         | 20.0 |
| Ovarian cyst  | 1               |                       |      | 1                     | 100.0 |           |      |
| Uterine prolapse with cystocele                                   | 3               | 1                     | 33.3 |                       |       | 2         | 66.6 |
| Total   | 30              | 13                    | 43.3 | 9                     | 30.0  | 8         | 26.7 |
| All cases with pelvic inflammation                                | 18              | 7                     | 38.9 | 7                     | 38.9  | 4         | 22.2 |
| Uncomplicated tumors (myomas and ovarian cysts)                   | 9               | 5                     | 55.5 | 2                     | 22.2  | 2         | 22.2 |

Of the 13 patients whose upper tracts returned to normal none had shown upper tract infection and only 3 had shown bladder infection in the original studies.

Of the 17 patients whose upper tracts failed to return to normal 3 had shown upper tract infections and 6 bladder infections in the original studies.

**TABLE IV. FOLLOW-UP STUDIES ON HYPERTENSION**

|   | GROUP I:<br>39 CASES<br>NO DILATATION<br>NO HYPERTENSION | GROUP II:<br>25 CASES<br>DILATATION<br>AND<br>HYPERTENSION  | GROUP III:<br>25 CASES<br>DILATATION<br>WITHOUT<br>HYPERTENSION | GROUP IV:<br>11 CASES<br>HYPERTENSION<br>WITHOUT<br>DILATATION |
|---|--|---|---|--|
| Definite hypertension. Systolic blood pressure above 160 and/or diastolic blood pressure above 95 | 0  | 14  | 0   | 5  |
| Borderline hypertension. Systolic blood pressure 140-160 and/or diastolic blood pressure 90-95    | 0  | 11  | 0   | 6  |
| Number followed   | 20   | 13<br>6 definite<br>7 borderline  | 14  | 2 definite<br>2 borderline                                     |
| Improved  |  | 1 definite to normal<br>1 definite to borderline<br>4 borderline to normal<br>2 definite temporarily or moderately improved |   |  |
| No change   | 19   | 1 definite<br>2 borderline  | 11  | 4  |
| Blood pressure increased  | 1 developed definite hypertension                        | 1 borderline to definite<br>1 definite and higher   | 2 normal to definite<br>1 normal to borderline                  |  |





Fig. 1.



Fig. 2.

Fig. 1.—Left retrograde pyelogram of a colored patient, aged 37 years, with uterine fibroids extending above the umbilicus. Intravenous pyelograms had shown similar dilatation of the right pelvis and ureter, but this plate was made because of poor visualization of the left tract by the excretory method. The patient's blood pressure at this time was; 226/132.

Fig. 2.—Bilateral retrograde pyelogram of the same patient illustrated in Fig. 1, six weeks after supravaginal hysteromyomectomy and left salpingo-oophorectomy. It can be noted that the urinary tracts have returned to essentially normal proportions. The patient's blood pressure had been reduced to 154/84 at the time of discharge from the hospital and was 195/110 when this plate was made. In the course of a year, however, it returned to its preoperative level.



Fig. 3.



Fig. 4.

Fig. 3.—Preoperative intravenous pyelograms of a colored woman, aged 43, with large uterine fibroids, chronic salpingitis and left ovarian abscess.

Fig. 4.—Preoperative retrograde pyelogram of the same patient as Fig. 3, made to obtain better visualization of the left urinary tract. The preoperative blood pressure was 144/80. Operation was supravaginal hysteromyomectomy, and bilateral salpingo-oophorectomy.



Fig. 5.

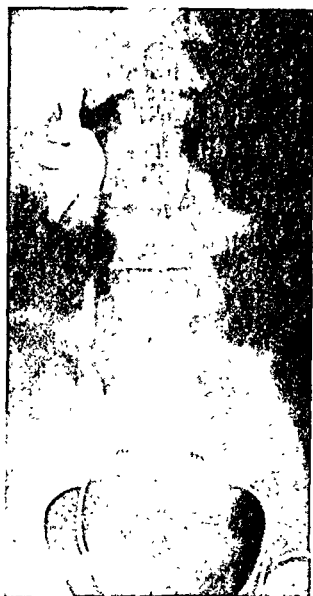


Fig. 6.

Fig. 5.—Retrograde right pyelogram of the same patient as illustrated in Figs. 3 and 4. Note the return to normal of the pelvis and ureter. On the left side, the one upon which the ovarian abscess had been situated, dilatation of the pelvis and ureter equal to that present preoperatively persisted. After 19 months the patient's blood pressure had increased to 150/100.

Fig. 6.—Right retrograde pyelogram of a colored woman, aged 53 years, with pelvic cellulitis and bilateral *E. coli* infection of the upper urinary tracts. There was marked diminution of the phenolsulphonephthalein output from both kidneys. She was treated with sulfanilamide and diathermy with resulting eradication of the urinary tract infection, return of the phenolsulphonephthalein output to normal, and marked improvement in the pelvic cellulitis. The blood pressure before treatment was normal 128/78.

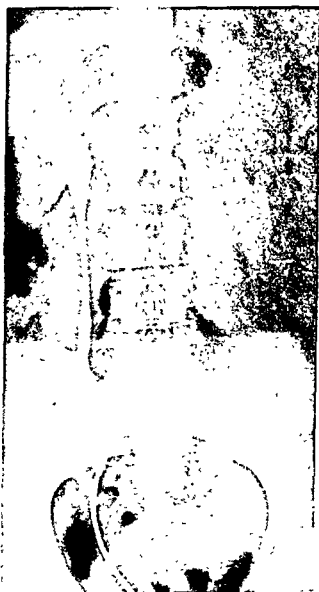


Fig. 7.—Posttreatment right pyelogram of the same patient as Fig. 6. There is some decrease in the size of the pelvis and ureter but definite dilatation is still present. On the left side, which was similar to the right before treatment, there was no decrease in size. After twenty months the patient's blood pressure had risen to 160/110.

Hypertension was classified as either definite or borderline, those patients with a systolic blood pressure of more than 160 and/or a diastolic pressure of more than 95 being assigned to the definite group. In the borderline group were included those patients with a systolic pressure of 140 to 160 and/or a diastolic pressure of 90 to 95.

The results of treatment upon the urinary tracts in 30 of the 50 patients who had shown pelvic and ureteral dilatation are shown in Table III. In Table IV are shown the results of blood pressure studies



Fig. 8.



Fig. 9.

Figs. 8 and 9.—Right and left pyelograms of a white patient, aged 64 years, with complete procidentia of eight years' duration. The preoperative blood pressure was 200/100. There was no change in the pyelograms following correction of the prolapse by the Richardson composite operation, but there was slight improvement in the hypertension, the blood pressure being 162/92 at the time of discharge from the hospital and 175/100 after nineteen months.

made from one to two years following completion of treatment. Table V is an attempt to correlate the follow-up studies on hypertension with those on the urinary tracts for the group, while Tables VI and VII show the details of some individual patients in this regard.

In addition to the 100 patients originally studied, a second hundred with pelvic masses at least sufficiently large to fill the cul-de-sac of Douglas, but who were not subjected to urologic examination, have been analyzed for the incidence of hypertension. This condition was found in 44 of this group, the average age of which was 39.4 years. In the total 200 patients studied, therefore, an incidence of 40 per cent of arterial hypertension was found. In Table VIII the incidence of hypertension according to race and age is analyzed and compared with a control group of 200 patients, 100 white and 100 colored, taken from

routine admissions to the gynecologic wards. Such a group of necessity includes a considerable number of patients with major gynecologic disorders, such as are being considered herein, but it also includes a sufficient number of patients without pelvic masses or uterine prolapse to make it worth while for the sake of comparison.

TABLE V. URINARY TRACT STUDIES IN PATIENTS FOLLOWED FOR HYPERTENSION

|  | ORIGINAL STUDY        |                     | FOLLOW-UP STUDY |        |                       |
|--|-----------------------|---------------------|-----------------|--------|-----------------------|
|  | INFECTED UPPER TRACTS | DIMINISHED FUNCTION | NO.             | NORMAL | PERSISTENT DILATATION |
| Group II: 8 cases improved                                   | 0                     | 3                   | 7               | 5      | 2                     |
| Group II: 5 cases with blood pressure unchanged or increased | 3                     | 2                   | 3               | 1      | 2                     |
| Group III: 3 cases which developed hypertension              | 2                     | 2                   | 3               | 1      | 2                     |
| Group III: 11 cases in which blood pressure remained normal  | 0                     | 0                   | 8               | 4      | 4                     |

In Table IX the incidence of hypertension in the two groups is shown in comparison with that found by Wetherby<sup>13</sup> in a group of 3,250 women. Wetherby has defined hypertension in this group to include all patients with a systolic blood pressure of 150 or more. He has made no division as to race, so for the purpose of comparison with his figures this division is omitted in our groups also. However, in analyzing our results it must be borne in mind that a large proportion, 77.5 per cent, of our patients were colored. In a study of 1,198 colored and 989 white hypertensive patients admitted to the Louisville City Hospital during the same period, Weiss and Prusmack<sup>14</sup> found that hypertension occurred a decade earlier in the negroes than in the whites.

#### DISCUSSION

Tables VIII and IX show conclusively that the incidence of hypertension in the group of patients under consideration is definitely higher than in two control groups of similar age. This difference is most striking in those patients from 30 to 39 years of age, and the incidence of the gynecologic disorders under consideration is also highest among patients falling into this age group. These findings taken alone are suggestive that these gynecologic disorders may play some etiologic role in the production of hypertension. The studies of the urinary tracts in the first 100 patients showed that the incidence of hypertension was more than twice as great in those patients who showed evidence of urinary tract stasis as in those in whom such stasis was absent. This finding is at least suggestive that if these gynecologic conditions do play an etiologic role in the production of hypertension, they probably do so as a result of their interference with the normal function of the urinary tracts.

TABLE VI. DETAILS OF 14 CASES FOLLOWED FOR HYPERTENSION IN GROUP II: UPPER TRACT DILATATION AND HYPERTENSION

|  | SERIES NO. | AGE | RACE | ORIGINAL DIAGNOSIS                                   | TREATMENT  | AMOUNT OF DILATATION | UPPER TRACT INFECTION | DIMINISHED FUNCTION | BLOOD PRESSURE |           |           | FOLLOW-UP OF URINARY TRACTS      |
|--|------------|-----|------|--|--|----------------------|-----------------------|---------------------|----------------|-----------|-----------|----------------------------------|
|  |            |     |      |  |  |                      |                       |                     | ADMISSION      | DISCHARGE | FOLLOW-UP |                                  |
| Definite hypertension returned to normal.<br>1 case      | 32         | 34  | c    | Adenomyoma<br>Salpingitis<br>chronic                 | Hysterectomy<br>Right<br>salpingo-<br>oophorectomy   | Right<br>+           | 0                     | 0                   | 144<br>102     |           | 120<br>80 | Not done                         |
|  | 4          | 45  | c    | Fibroids<br>Salpingitis<br>chronic                   | Hysterectomy<br>Right<br>salpingo-<br>oophorectomy<br>Left sal-<br>pingectomy                  | Bilateral<br>+++     | 0                     | 0                   | 132<br>95      | 122<br>85 | 110<br>78 | Normal                           |
| 4 cases with borderline hypertension returned to normal. | 19         | 44  | c    | Adenomyoma<br>Tuboovarian in-<br>flammatory<br>cysts | Hysterectomy<br>Bilateral<br>salpingo-<br>oophorectomy   | Bilateral<br>++      | 0                     | 0                   | 135<br>90      |           | 110<br>80 | Normal                           |
|  | 75         | 21  | c    | Pelvic abscess                                       | Laparotomy<br>with drainage<br>twice<br>Hysterectomy<br>Bilateral<br>salpingo-<br>oophorectomy | Right<br>+++         | 0                     | Right               | 140<br>90      | 130<br>80 | 118<br>70 | Normal                           |
|  | 85         | 20  | c    | Pelvic abscess                                       | Posterior<br>colpotomy   | Bilateral<br>+++     | 0                     | 0                   | 140<br>80      |           | 124<br>84 | Right, normal<br>Left, no change |

wife was a universal donor and the husband belonged to Group A (international classification). It was thought that the blood (or other tissues) of the developing fetus might be incompatible with the mother, and that intramuscular injections of the husband's blood might help to neutralize the effect on the mother of the developing tissues (probably the blood in particular). The effect was usually evident within an hour of the injection.

Eighth pregnancy: Nausea similar to previous pregnancies began about the fourth week after conception. On Sept. 23, 1940, 2.5 c.c. of the husband's blood were given intramuscularly one evening. The next morning the patient was able to get up and have breakfast for the first time in a week. The relief lasted about six days when mild nausea re-

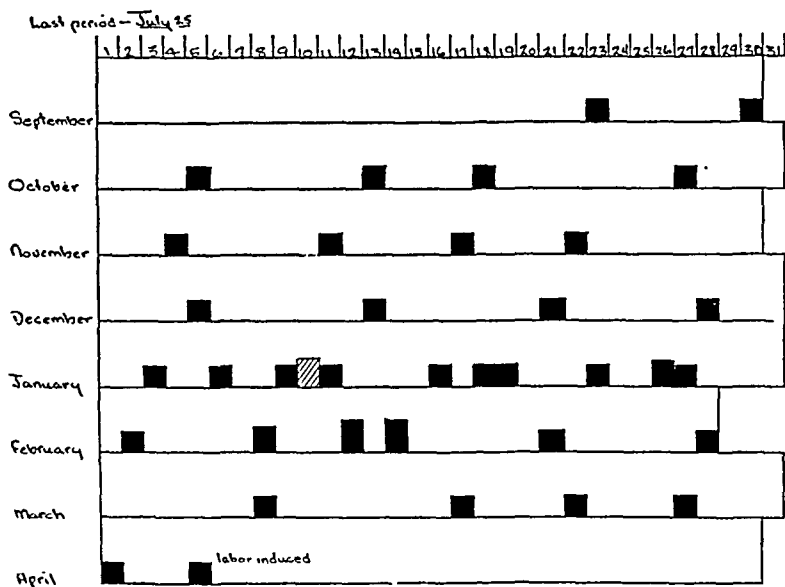


Fig. 1.—Husband's blood given intramuscularly in doses of  $2\frac{1}{2}$  to  $3\frac{1}{2}$  c.c. as frequently as necessary, depending on the patient's symptoms. Each square represents one injection. The crossed square, January 10, represents  $3\frac{1}{2}$  c.c. of patient's own blood.

turned. A second dose on September 30 brought similar relief. It was found necessary to repeat the injections every three to eight days, throughout the entire pregnancy, the longest interval being two weeks (Fig. 1).

The relief was striking and constantly repeated with each dose. It did not seem to make any difference what time of day it was given. When given while the patient was up and about, the effect was noticeable within an hour or two. The patient did have some heartburn which was not relieved by the blood injections.

Having seen two articles in which autohemotherapy<sup>6, 7</sup> was reported as giving relief from the nausea of pregnancy, it was decided (for one of the injections) to substitute 3 c.c. of the patient's own blood for the husband's to determine if this would give relief. No relief followed this injection, so the next day 2.5 c.c. of the husband's blood were given with relief that lasted five days.

The pregnancy advanced to the twenty-first week, Jan. 3, 1941, when a miscarriage was threatened. There were severe rhythmic uterine con-

TABLE VII. DETAILS OF 14 CASES FOLLOWED FOR HYPERTENSION IN GROUP III; DILATATION WITHOUT HYPERTENSION

|  | SERIES NO. | AGE | RACE | ORIGINAL DIAGNOSIS                                      | TREATMENT   | AMOUNT OF DILATATION | UPPER TRACT INFECTION | DIMINISHED FUNCTION | BLOOD PRESSURE |            | FOLLOW-UP OF URINARY TRACTS   |
|--|------------|-----|------|---|---|----------------------|-----------------------|---------------------|----------------|------------|---|
|  |            |     |      |   |   |                      |                       |                     | ORIGINAL       | FOLLOW-UP  |   |
| 3 developed hypertension<br>2 definite<br>1 borderline | 17         | 53  | c    | Subacute salpingitis. Pelvic cellulitis                 | Diathermy. Sulfanilamide                                      | Bilateral +++        | Bilateral             | Bilateral           | 128<br>78      | 160<br>110 | 20 mo.<br>No change left. Partial regression right. Function normal |
|  | 71         | 41  | w    | Adenomyoma  | Panhysterectomy   | Right +              | 0                     | Right               | 134<br>80      | 152<br>92  | 16 mo. No change  |
|  | 74         | 34  | c    | Fibroids. Right ovarian cyst. Right broad ligament cyst | Hysterectomy. Right salpingo-oophorectomy                     | Right +++<br>Left +  | Right                 | 0                   | 130<br>85      | 154<br>100 | 15 mo. Normal   |
| 11 patients whose blood pressure remained normal       | 22         | 32  | c    | Fibroids  | Hysterectomy. Left salpingo-oophorectomy                      | Bilateral +          | 0                     | 0                   | 120<br>85      | 108<br>70  | 19 mo. Normal   |
|  | 44         | 34  | c    | Subacute salpingitis                                    | Hysterectomy. Left salpingo-oophorectomy. Right salpingectomy | Right +              | 0                     | 0                   | 120<br>75      | 118<br>75  | 13 mo. Normal   |
|  | 69         | 27  | w    | Ovarian cyst, right                                     | Right salpingo-oophorectomy                                   | Bilateral +++        | 0                     | 0                   | 100<br>70      | 104<br>58  | 16 mo. Nearly normal  |

| Improved from<br>definite to bor-<br>derline group   | 41 | 55 | w | Prolapse,<br>second degree  | Manchester<br>operation                                   | Bilateral        | 0     | 0         | 194<br>104 |            | 160<br>94                | 16 mo.          | Normal  |
|--|----|----|---|---|---|------------------|-------|-----------|------------|------------|--------------------------|-----------------|---|
| 3 cases with def-<br>inite hyperten-<br>sion improved. 1<br>became border-<br>line. 2 remained<br>definite | 18 | 40 | c | Fibroids. Tubo-<br>ovarian in-<br>flammatory<br>cysts                               | Hysterectomy<br>Bilateral<br>salpingo-<br>oophorectomy    | Bilateral<br>+   | 0     | 0         | 170<br>110 | 134<br>90  | 130<br>70<br>154<br>104  | 4 mo.<br>19 mo. | No change   |
|  | 5  | 37 | c | Fibroids  | Hysterectomy<br>Left salpingo-<br>oophorectomy            | Bilateral<br>+++ | 0     | Bilateral | 226<br>132 | 154<br>84  | 195<br>110<br>225<br>115 | 6 wk.<br>8 mo.  | Pyelograms<br>normal. Func-<br>tion still di-<br>minished               |
|  | 8  | 64 | w | Complete<br>procidentia   | Richardson's<br>composite<br>operation for<br>prolapse    | Bilateral<br>+++ | 0     | Right     | 200<br>100 | 162<br>92  | 175<br>100               | 19 mo.          | No change in<br>x-rays. Func-<br>tion normal.<br>Cultures posi-<br>tive |
|  | 16 | 48 | w | Fibroids, bi-<br>lateral hydro-<br>salpinx. Car-<br>cinoma of<br>cervix. Stage<br>I | Panhysterectomy<br>Bilateral<br>salpingo-<br>oophorectomy | Left<br>+        | 0     | 0         | 145<br>78  |            | 160<br>68                | 19 mo.          | No change   |
| 2 cases with in-<br>creased hyperten-<br>sion  | 23 | 39 | c | Fibroids<br>Bilateral pyo-<br>salpinx   | Hysterectomy<br>Bilateral<br>salpingectomy                | Bilateral<br>+   | 0     | 0         | 155<br>85  |            | 144<br>94                | 16 mo.          | Normal  |
|  | 40 | 68 | w | Complete<br>procidentia   | Pessary. No<br>operation                                  | Right<br>++      | Right | 0         | 188<br>120 | 180<br>112 | 198<br>120               | 18 mo.          | Not done  |
|  | 6  | 43 | c | Fibroids<br>Ovarian abscess   | Hysterectomy<br>Bilateral<br>salpingo-<br>oophorectomy    | Bilateral<br>+++ | +     | Bilateral | 144<br>80  |            | 152<br>100               | 19 mo.          | Right, normal.<br>Persistent in-<br>fection. Left,<br>no change         |
|  | 38 | 35 | c | Fibroids  | Hysterectomy  | Right<br>++      | +     | +         | 190<br>110 | 160<br>100 | 210<br>140               | 17 mo.          | Not done  |



TABLE VIII. COMPARISON OF THE INCIDENCE OF HYPERTENSION ACCORDING TO AGE AND RACE IN THE 200 PATIENTS STUDIED AND 200 CONTROLS

| AGE      | WHITE        |         |                  |         |                       |         |              |         |                  |         | COLORED               |         |       |         |
|----------|--------------|---------|------------------|---------|-----------------------|---------|--------------|---------|------------------|---------|-----------------------|---------|-------|---------|
|          | NO. OF CASES |         | NO. HYPERTENSIVE |         | PER CENT HYPERTENSIVE |         | NO. OF CASES |         | NO. HYPERTENSIVE |         | PER CENT HYPERTENSIVE |         | STUDY | CONTROL |
|          |              |         |                  |         |                       |         |              |         |                  |         |                       |         |       |         |
|          | STUDY        | CONTROL | STUDY            | CONTROL | STUDY                 | CONTROL | STUDY        | CONTROL | STUDY            | CONTROL | STUDY                 | CONTROL | STUDY | CONTROL |
| Under 20 | 0            | 0       | —                | —       | —                     | —       | 2            | 0       | 1                | —       | —                     | —       | 50    | —       |
| 20-29    | 6            | 6       | 0                | 0       | 0                     | 0       | 26           | 13      | 4                | 3       | —                     | —       | 15.2  | 23      |
| 30-39    | 14           | 33      | 2                | 2       | 14.3                  | 6.06    | 68           | 41      | 25               | 10      | —                     | —       | 36.8  | 24.4    |
| 40-49    | 15           | 27      | 5                | 8       | 33.3                  | 29.6    | 49           | 31      | 27               | 7       | —                     | —       | 55.1  | 22.6    |
| 50-59    | 7            | 18      | 6                | 9       | 85.7                  | 50.0    | 9            | 10      | 6                | 7       | —                     | —       | 66.7  | 70.0    |
| 60-69    | 3            | 10      | 3                | 5       | 100.0                 | 50.0    | 1            | 4       | 1                | 3       | —                     | —       | 100.0 | 75.0    |
| 70-79    | 0            | 6       | —                | 2       | —                     | 33.3    | 0            | 1       | —                | 1       | —                     | —       | —     | 100.0   |
| Total    | 45           | 100     | 16               | 26      | 35.5                  | 26.0    | 155          | 100     | 64               | 31      | —                     | —       | 41.3  | 31.0    |

|    |    |   |   |   |              |   |   |                  |                  |        |   |
|----|----|---|---|---|--------------|---|---|------------------|------------------|--------|---|
| 68 | 38 | c | Subacute salpingitis. Tuboovarian abscess, left | Sulfanilamide. Diathermy                                      | Left +       | 0 | 0 | $\frac{132}{78}$ | $\frac{110}{70}$ | 18 mo. | Nearly normal                             |
| 67 | 33 | c | Pelvic cyst, inflammatory                       | Posterior colpotomy   | Right +++    | 0 | 0 | $\frac{118}{82}$ | $\frac{124}{68}$ | 18 mo. | Moderate decrease                         |
| 31 | 27 | c | Fibroids. Chronic salpingitis                   | Hysterectomy. Bilateral salpingo-oophorectomy                 | Bilateral ++ | 0 | 0 | $\frac{110}{80}$ | $\frac{118}{86}$ | 18 mo. | Moderate decrease, right. No change, left |
| 78 | 21 | c | Chronic salpingitis. Cystic ovary, left         | Hysterectomy. Left salpingo-oophorectomy. Right salpingectomy | Right +      | 0 | 0 | $\frac{130}{80}$ | $\frac{120}{70}$ | 15 mo. | No change                                 |
| 99 | 37 | w | Retroversion. First-degree descensus            | Richardson's composite operation for prolapse                 | Right ++     | 0 | 0 | $\frac{118}{72}$ | $\frac{118}{86}$ | 15 mo. | No change                                 |
| 46 | 37 | c | Bilateral tuboovarian abscess                   | Abdominal drainage, right abscess                             | Bilateral ++ | 0 | 0 | $\frac{138}{82}$ | $\frac{120}{80}$ | 16 mo. | Not done                                  |
| 65 | 38 | c | Chronic bilateral salpingitis                   | Diathermy   | Right +      | 0 | 0 | $\frac{135}{80}$ | $\frac{122}{72}$ | 21 mo. | Not done                                  |
| 81 | 44 | c | Fibroids  | Hysterectomy. Left salpingo-oophorectomy                      | Right +      | 0 | 0 | $\frac{120}{78}$ | $\frac{118}{70}$ | 16 mo. | Not done                                  |

ureter, subjected to pressure over a long period of time by a pelvic mass or a prolapsed uterine vessel, might undergo fibrotic changes resulting in stricture formation sufficient to prevent its return to normal after removal of the original cause of compression. Then too, in some instances intrinsic strictures may have developed independently of the gynecologic lesions. In the group of patients studied, however, the symptoms of ureteral stricture so often detailed and stressed by Hunner have been conspicuously absent. We therefore feel that in the case of pelvic inflammatory disease and the lesser degrees of uterine prolapse especially, surgical intervention should not be too long delayed. If in patients with pelvic inflammation, masses persist after a sufficient conservative regime of palliation and chemotherapy to produce abatement of signs and symptoms of acute inflammation, these masses should be removed. In young women with relaxation of the pelvic floor and moderate uterine prolapse, repair operations of conservative types, compatible with future childbearing, should be carried out in preference to delaying operation until the patients' families are complete in order to do more radical procedures.

#### CONCLUSIONS

We believe that the foregoing study warrants the following conclusions:

1. That arterial hypertension occurs with greater frequency in patients suffering from various types of large pelvic masses and from uterine prolapse than it does generally in women of similar age.

2. That the hypertension in such a group probably results frequently from interference with normal ureteral drainage caused by the gynecologic lesion in question.

3. That the therapy selected for the treatment of such gynecologic lesions should be of a type that tends to relieve as completely as possible such interference with ureteral drainage; namely, surgical removal of the pelvic masses and adequate repair of uterine prolapse.

4. That such therapy should not be delayed too long merely because of the absence of marked symptoms on the part of the patient.

The diodrast used for intravenous urography in these studies was furnished by the Winthrop Chemical Company.

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8. Crabtree, E. Granville, and Chaset, Nathan: *Ibid.* 115: 1842, 1940.
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TABLE IX. COMPARISON OF PERCENTAGE INCIDENCE OF HYPERTENSION BY AGE DECADES IN 200 PATIENTS STUDIED, AUTHOR'S CONTROLS, AND 3,250 WOMEN REPORTED BY WETHERBY

| AGE      | SERIES STUDIED | AUTHOR'S CONTROL | 3,250 WOMEN<br>WETHERBY |
|----------|----------------|------------------|-------------------------|
| Under 20 | 50.0           |                  | 1.05                    |
| 20-29    | 12.5           | 15.8             | 3.01                    |
| 30-39    | 32.9           | 17.6             | 10.33                   |
| 40-49    | 50.0           | 25.9             | 40.89                   |
| 50-59    | 75.0           | 57.1             | 50.50                   |
| 60-69    | 100.0          | 57.0             | 66.82                   |
| 70-79    |                |                  |                         |

We feel that such a concept may offer a possible explanation for the syndrome sometimes referred to as "myoma heart," which has hitherto not been adequately explained. We furthermore feel that in planning gynecologic treatment for patients suffering from such diseases as tend to interfere with the normal function of the urinary tract, therapeutic methods should be chosen which tend as nearly as possible to remove completely such interference. This we believe is particularly pertinent regarding the selection of operation or irradiation therapy for uterine fibroids. The latter type of therapy, although it may relieve the obvious symptoms of fibroids such as uterine bleeding, does not remove the tumors. Furthermore, as has been shown previously in two publications by one of us (Everett<sup>15, 16</sup>), this type of therapy per se sometimes results in fibrosis with stricture formation in the lower ureters. We, therefore, feel that before selecting irradiation therapy for uterine fibroids, the presence of hydronephrosis and hydroureter should be eliminated by intravenous urography, and indeed that probably the best policy is to confine such therapy to that relatively small group of patients in whom there is some absolute contraindication to surgical intervention. Furthermore, it is not unusual to encounter patients near the menopausal age with uterine fibroids which are producing no symptoms. It has been our tendency in the past to defer operation with the assurance that if the condition remains asymptomatic until the menopause is fully established no further trouble is likely to ensue. We now feel that before such a policy is decided upon, the absence of ureteral compression by the fibroid masses should be determined by means of intravenous urography.

In Table III an attempt was made to find some common factor such as the presence of urinary tract infection or of pelvic inflammation which might explain the failure of the urinary tracts to return to normal following appropriate gynecologic treatment. Neither of these factors seemed to answer this question adequately, and although it is difficult to show statistically or in tabulated form, it has been our impression from studying the patients individually that a very important factor in this regard is the length of time over which the gynecologic lesions in question have persisted. It is conceivable that a segment of

## GONORRHEA IN THE FEMALE AND ITS TREATMENT WITH SULFONAMIDES\*

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SOME of the earliest medical writings make mention, in both man and woman, of the disease we now know as gonorrhea. It remained, however, for Neisser (1879) to identify and Bumm (1885) to culture the specific microorganism. Vonderlehr and Usilton<sup>1</sup> of the United States Public Health Service stated in 1937 that at least one million persons in this country acquire gonorrhea each year, of whom approximately one-fourth (230,000) are women. During the past four years there has been approximately three to four thousand female cases reported in New York City each year. It is felt by responsible officials that this record is far from complete.

A knowledge of the natural course of this disease is essential in the interpretation of therapeutic measures. It is probable that in many cases the disease remains localized to the lower genitourinary tract and does not invade beyond the depth of the mucous membrane surfaces. Furthermore, in the majority of these patients the infection gradually and spontaneously dies out in these sites. The urethra is usually cured first and the time necessary for spontaneous cure probably varies from a few weeks to even years in some cases. Invasion of the upper genital tract most frequently follows menstruation, the termination of a pregnancy, or the application of physical and chemical agents employed in treatment. It is quite uncommon for the infection to persist for any long period of time in the Fallopian tubes or peritoneal cavity. Our experience in this respect is, in general, in agreement with that of Curtis,<sup>2</sup> which was reported twenty years ago. In our opinion the use of local antiseptics and other older methods of treatment rarely affected favorably the clinical course and, at times, they initiated extension of the disease that later caused irreparable damage. The acceptance of these facts means that we are not dealing with a fatal disease and accordingly any therapy must be absolutely safe.

Specific fever therapy, based on the thermal death time of the infecting strain of gonococcus, was introduced by Carpenter and his associates<sup>3</sup> in 1932 and constituted the first really specific therapy employed in the treatment of this disease. Carpenter and others<sup>4</sup> have reported over

\*Read, by invitation, at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.

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## DISCUSSION

DR. ROBERT A. KIMBROUGH, PHILADELPHIA, PA.—In view of an increasing amount of evidence there can be little doubt that the various obstructive uropathies not infrequently cause arterial hypertension. This fact is attested not only by the occurrence of hypertension in this group of cases but by the improvement or actual relief of hypertension after the obstructive lesions have been eliminated.

The series of cases presented by Dr. Everett, while not extensive, is sufficiently large and so carefully studied that it constitutes an important contribution to this chain of evidence. One wonders, however, whether more detailed investigation might not have revealed other more likely causes for hypertension in some of his patients.

The high incidence of both hypertension and ureteral obstruction in this rather ordinary run of gynecologic cases constitutes a potent reason for early removal of pelvic masses and not too long delayed correction of prolapsus.

I am sure that many of us have chosen irradiation therapy for hypertensive patients with large myomas rather than subject them to the risks of surgical removal. In view of this study we possibly have been withholding from such patients the best chance of relieving their hypertension. It would seem quite reasonable in these cases, as Dr. Everett has suggested, that surgical removal of large myomas is indicated either as prophylaxis against or treatment of the accompanying urinary stasis and hypertension.

DR. EVERETT (closing).—I had no intention of indicating that hypertension had been relieved to any great extent, although this seems to have happened in a few patients. The number of cases in which this occurred, however, was too small to make that deduction of much value. To predict the relief of hypertension in individual cases would be very difficult.

The causes of hypertension of renal origin are so involved with the anatomy and physiology of the kidney that those who have done the most work on the subject, particularly Page, believe that hypertension is largely due to inadequate or impaired blood supply of the kidney. According to the work of Goldblatt, this usually results from some compression of the arterial blood supply.

There are several methods, rather complicated ones, of determining the diminution of the blood supply. Howard Taylor has recently reported a series of patients with obstetric toxemias, in which he studied the comparison of the inulin and diodrast clearance tests. Diminution of tubular function, as indicated by a decreased diodrast clearance, is supposed to show a diminution of blood supply to the tubular epithelium which results in the secretion into the system of pressor substances. These tests are usually done on the total renal substance representing both kidneys. In cases where the surgical relief of hypertension is proposed, a better idea of the prognosis may be obtained by differential inulin and diodrast clearance tests performed on the individual kidneys. I have carried out such procedures in a few cases, but they are almost too tedious and time-consuming to apply to a large series.

A study of such factors as age, color, marital status, and the incidence of pregnancy prior to, during, and following treatment revealed no important differences in the three groups. Fig. 1 illustrates the distribution of patients with respect to the nature of the infection. The number thought to have acute initial infections was practically the same in each group. There was a somewhat larger number of chronic infections in the sulfanilamide group. Most instances of recurrence of the disease were treated with sulfathiazole or sulfadiazine for reasons that will later become evident. Fig. 2 demonstrates the close similarity in the three groups as far as the site of disease is concerned. Nearly 60 per cent of the entire group were thought to have the disease confined entirely to the lower genitourinary tract. It was impossible to demonstrate the presence of the disease in the genital tract in one of two patients who had suppurative arthritis despite repeated positive cultures from the joint exudate.

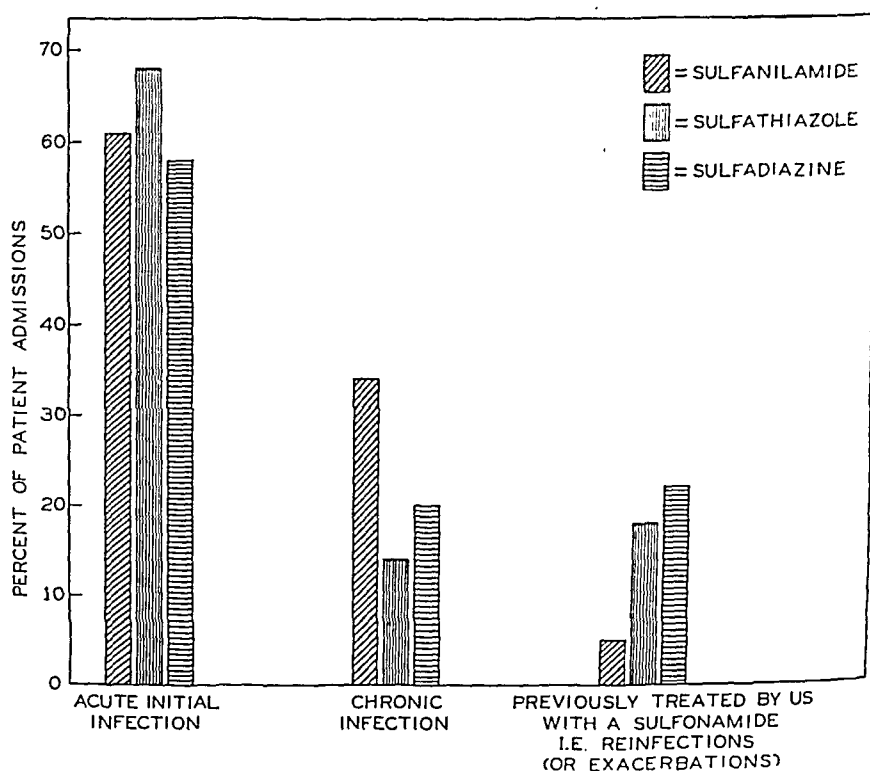


Fig. 1.—Nature of infection.

Serologic or other positive evidence of syphilis was present at the time of admission on 19 occasions (10.3 per cent), four instances in each of the sulfanilamide and sulfadiazine groups and 11 times in the sulfathiazole group. A few patients were admitted with early infectious syphilis and for the most part were treated for that disease until they were rendered noninfectious before instituting the sulfonamide therapy.

#### DIAGNOSIS

The diagnosis of gonorrhea has long been a difficult, and in some respects, a controversial problem. It is true that a clinical history

80 per cent of cures where this principle was adhered to following a single treatment. The method, however, is now employed only to a very limited extent and chiefly in the treatment of sulfonamide failures. Clinical reports on the use of sulfanilamide started appearing during the summer of 1937 and have since completely revolutionized our therapeutic armamentarium. Our investigations with this compound were commenced shortly thereafter. Sulfathiazole in late 1939 and sulfadiazine in 1940 were introduced for clinical investigation and were at once employed in the studies to be reported. While there have been many favorable clinical reports on the use of the former drug in gonorrhea very few on the use of the latter compound have as yet appeared in the literature. The advent of these newer methods of treatment has aroused much interest and the imagination of many public health officials has been stirred to the point where they now believe it possible to eliminate this most prevalent of all infectious diseases. With these facts in mind it would appear to be an appropriate time to review some phases of our work on this problem.

It is our purpose to detail our experiences from two main points of view. The first has reference to diagnosis and an attempt will be made to correlate subjective symptoms and signs with more exact laboratory studies. Data will be presented, demonstrating the superiority of cultural methods as compared to the study of smears. The second problem deals largely with therapy and is confined entirely to the evaluation of three drugs, i.e., sulfanilamide, sulfathiazole, and sulfadiazine. Variations in dosage, duration of treatment, the effect of various social and economic factors, pregnancy, race, age, and other differences will be considered briefly. Toxicity and dangers associated with the administration of the various drugs will be commented upon.

The study is based upon observations made on 185 admissions to the New York Lying-in Hospital of 158 patients all of whom had gonorrhea. Twenty-five patients were admitted a second time and two on a third occasion. Patients not admitted or where there was any question as to the diagnosis are excluded from the present study. Sixty-four patients were treated with sulfanilamide, 62 with sulfathiazole, and 59 with sulfadiazine. In the charts that follow the three groups are designated according to the sulfonamide employed irrespective of whether the data have reference to therapy or not. Dosage, toxic symptoms, fluid balance, blood and urine studies, and social behavior were all known factors, many of which are undeterminable in the case of ambulatory patients. A comparison of factors, such as age, color, site of disease, etc., is necessary because at the time the study was started only sulfanilamide, of the drugs employed, was available. The other compounds were used as they were introduced for investigational purposes, and accordingly it was not possible to alternate patients at the time of admission with respect to the drug employed.



tractions. This was controlled by luminal sodium, 5 gr., and proluton, 0.2 mg., given intramuscularly and codeine 2 gr. subcutaneously. It was necessary to repeat this procedure three times subsequently, January 5, 29, and February 12.

The patient was able to be up and about throughout all but the last six weeks of the last pregnancy which was in striking contrast to the seven previous gestations. She even took several train, car, and plane trips, totaling almost 4,000 miles during the second and third months of gestation. At the thirty-sixth week the patient began to feel badly and the blood pressure rose from the usual 100/70 to 120/80 with general malaise and mental depression. The urea in the blood was slightly elevated, and it was thought that the patient was threatened with an atypical toxemia. Labor was, therefore, induced on April 5, 1941, and a well-developed female child was born April 6, 1941. The only abnormality noted was a moderate jaundice which cleared up in about three weeks.

The report on the blood groupings was as follows:

Baby's blood: 4/7/41, Taken the day after birth. Type A (international classification).

Father's blood was the same group, and there was no cross agglutination after one-half hour.

Mother's blood belonged to Group O (international classification).

The microscopic cross-agglutination test showed agglutination of daughter's cells by the mother's serum and no agglutination of the mother's cells by the daughter's serum after one-half hour. Thus, it is seen that the newly forming blood and probably other tissues of the developing fetus were actually incompatible, at least with the mother's blood.

Thinking that the Rh factor iso-immunization might account for some of the pathology, tests were carried out on the parents. It was found that the father's blood was Rh negative and the mother's and baby's bloods Rh positive, thus excluding the possibility that there could be any iso-immunization factor as a cause of the hyperemesis. Tests for another antigen, work in which is to be published shortly, were carried out. This antigen which has just been brought to light may possibly have been a factor in the present case as the father's and baby's bloods were positive and the mother's was negative.

#### COMMENTS

It is worthy of note that the patient had been allergic to certain foods for several years. She would suffer from severe incapacitating headaches requiring 2 to 3 gr. of codeine by hypodermic to control them. The headaches occurred six to eight hours after taking such articles of diet as coffee, chocolate, peas, maple syrup, and cow's milk and cream. She was extremely sensitive to paprika, having had attacks of pulmonary edema on three different occasions. These reactions were unaltered by the pregnancy, but most interesting was the fact that she began to have a return of this severe type of headache during the pregnancy without taking any food to which she was known to be sensitive. It was found that when the husband had taken any of the foods to which she was sensitive that a headache followed the injection of his blood within two or three hours. After the twentieth week, the

correlated with the physical findings may be very suggestive. The complement fixation test has largely fallen into disrepute in this country. Torrey,<sup>5</sup> on the other hand, still feels that it is a highly specific diagnostic aid, if the antigen is of high sensitivity, low in anticomplimentary property and all proper precautions in conducting the test are exercised. Assuming this to be true many negative tests during the early stages and many positive reactions after the cure of the disease would almost certainly be obtained. These points become especially significant at the present time in the control of treatment when the disease may actually be cured in a matter of hours. Thus from a laboratory point of view we are confined largely to the use of smears and cultures.

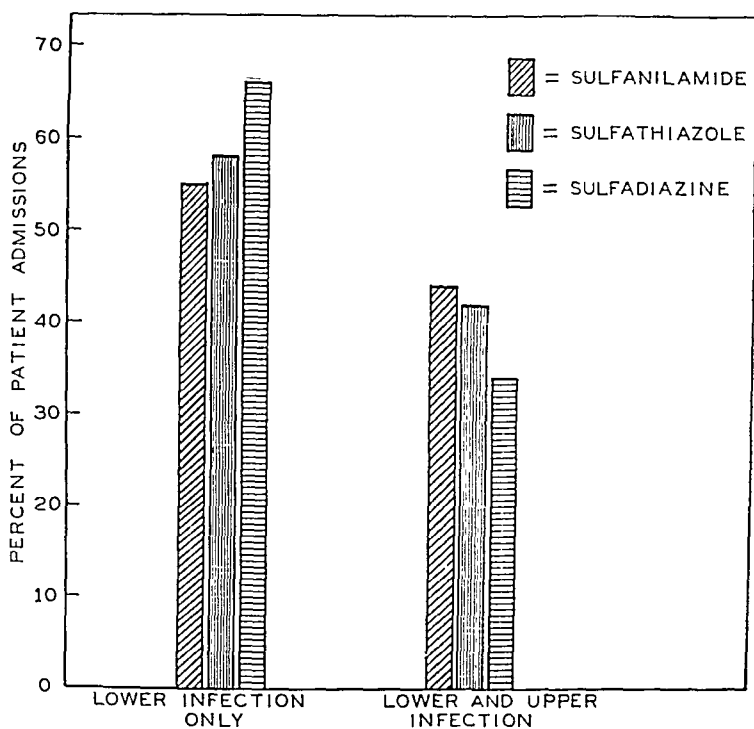


Fig. 2.—Site of disease.

#### ROUTINE EMPLOYED

With adequate exposure of the vulva and a good source of light, the labia are held far apart, bringing the external urethral meatus into view. The area just within the meatus is first cleaned with a sterile applicator which is then discarded. The urethra is massaged from back forward and from either side to the midline. The exudate so expressed is collected on a small, moist sterile swab. Smears are prepared by the "rolling technique" on clean glass slides, and after reapplying the swab to the urethra it is plated directly on a chocolate agar plate (Difco\*). Cervical exudate for similar studies is obtained from the endocervix after cleaning the vaginal vault with a sterile cotton ball. In the event that bacteriologic quantitative determinations are desired, the technique is the same, excepting the swab is rotated three complete turns in either the urethra or cervix. The swab is then inoculated and

\*Difco Laboratories, Incorporated, Detroit, Michigan.

emulsified in 0.5 c.c. of Douglas broth and 0.2 c.c. of the suspension is then inoculated on the surface of the plates.

The laboratory procedure used is essentially the modification by Leahy and Carpenter,<sup>6</sup> of the technique proposed by McLeod and his co-authors.<sup>7</sup>

All smears were stained by Gram's method. With respect to the interpretation of smears a "positive" implies the organisms to be intracellular and otherwise characteristic. The chocolate agar plates were placed in an inverted position in airtight jars, replacing approximately 12 per cent of the air with 10 per cent carbon dioxide.

Observations of cultures were made at the end of a forty-eight hour incubation period at 37° C.; smears were made of the typical colonies and stained by Gram's method. Frequently in the case of initial cultures the colonies were subcultured to carbohydrate media for the fermentation reaction to ascertain final confirmation.

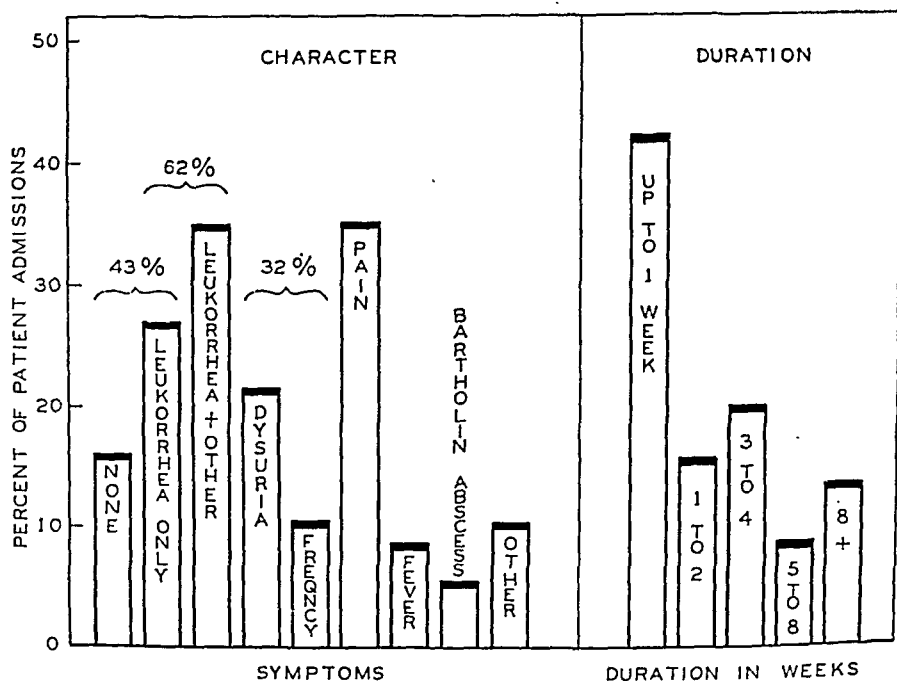


Fig. 3.—Symptoms on admission (entire series).

All subsequent cultures were examined by the oxydase reaction described by McLeod, et al.<sup>7</sup> The reagent is applied by pipetting 1 to 2 c.c. of a 1 per cent aqueous solution of p-aminodimethyl aniline monohydrochloride.\* The plate is observed for evidence of color changes in the colonies. The color reactions occurring in sequence are pink, maroon, and finally black with intermediary changes. Smears are then made and stained by Gram's method.

Since the dye is toxic for the gonococcus, if subcultures are desired, it is necessary to transfer the suspected colony in the pink stage. The oxidation progressing to the black stage of the colony will render the cells nonviable, therefore, preventing growth in subculture. However, the dye does not interfere with Gram's stain.

\*Eastman Kodak Company, Rochester, New York.

Fig. 3 illustrates the frequency of the occurrence of the more common symptoms. It is significant to note that 16 per cent had no complaints and an additional 27 per cent gave leucorrhea as their only symptom, a total of 43 per cent. Urinary tract symptoms were present in one-third and abdominal pain was complained of in approximately an equal number of cases. The patients without symptoms were discovered, for the most part, through epidemiologic studies carried out by the Department of Health of New York City, and referred to us for treatment. The duration of symptoms played no role as far as we could determine in the therapeutic results.

In Fig. 4 the diagnostic results of smear and culture studies are displayed. The first section of the chart is based on an analysis of the results of the first specimen *only* obtained from each patient. The similarity of results in each of the groups is striking. If the data are

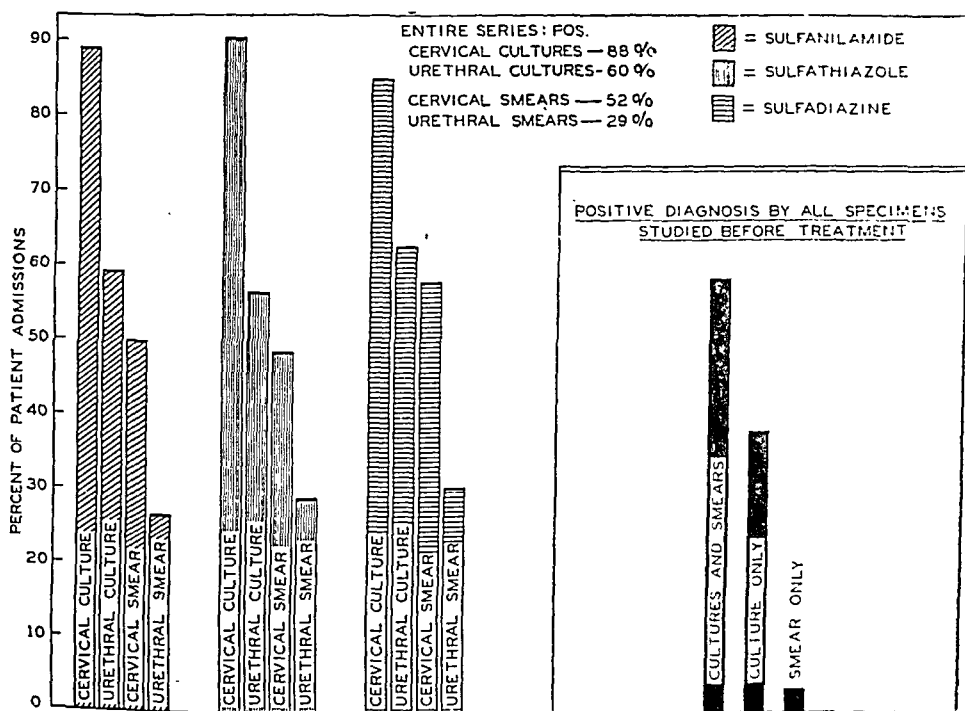


Fig. 4.—Positive diagnosis by first specimen studied before treatment.

combined and approximations employed we may say that nine-tenths of the cervical cultures and only one-half of the cervical smears were positive. Sixty per cent of the urethral cultures and one-half that number of urethral smears were found to be positive.

If we study the results of *all* cultures and smears taken before the onset of treatment we may say that a positive laboratory diagnosis was based on both positive cultures and smears in nearly 60 per cent, on positive cultures *only* in over 35 per cent and positive smears alone in a relatively insignificant number of cases. In addition, a number of the smears revealed extracellular forms and might be designated "suspicious" but are rightfully excluded from the positive group. Even if

these were included they would raise the positive cervical smears but 12 per cent and the urethral smears 9 per cent.

Fig. 5 illustrates the results of all cultures and smears employed in the diagnosis, control of treatment, and in follow-up studies. These data are based on a total of 8,765 laboratory procedures. Many negative specimens are introduced by this means of analysis so that the number of positive results appears relatively small. However, the essential differences, as far as the relative value of the four procedures with relation to positives, are maintained. Therefore, it becomes evident that if cultures are omitted from any diagnostic routine, approximately 35 per cent of patients who actually have the disease will be undiagnosed.

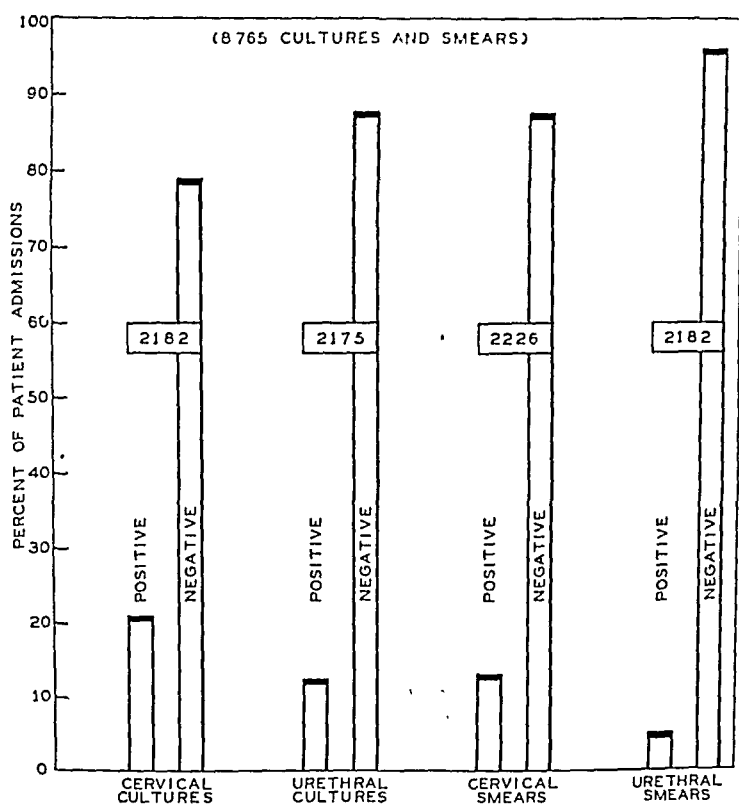


Fig. 5.—Results of all cultures and smears employed in diagnosis control of treatment and follow-up.

If suspicious cases are included as positive, this percentage would be reduced to approximately 25 per cent. Many of the cases recognized by cultural methods only are likely to be chronic "carriers" who, for the most part, may be asymptomatic, and it is this group which constitutes a serious public health problem. In general it may be said that either smears or cultures will usually give positive results in the acute exudative stage of the process but for the accurate diagnosis of the latent phase of the disease cultural methods should be employed.

#### TREATMENT

The duration of hospitalization was frequently considerably longer than actually necessary in order to repeat diagnostic procedures and

to make many other observations that seemed desirable for this study. In general, however, it may be seen from Fig. 6 that the sulfanilamide group was hospitalized appreciably longer than the other two groups. In fact, two-thirds of the sulfathiazole and sulfadiazine groups were discharged by the tenth day at which time only one-fourth of the sulfanilamide group were permitted to leave. We feel that hospitalization for therapy is highly desirable but not absolutely essential.

In over 80 per cent of instances treatment was started within nine days from the time the diagnosis was made. Delay was chiefly due to locating patients, repetition of diagnostic procedures and the treatment of infectious syphilis prior to the institution of sulfonamide therapy. In our experience, we found no correlation between the specificity of the therapy and the duration of symptoms or the interval from diagnosis to treatment.

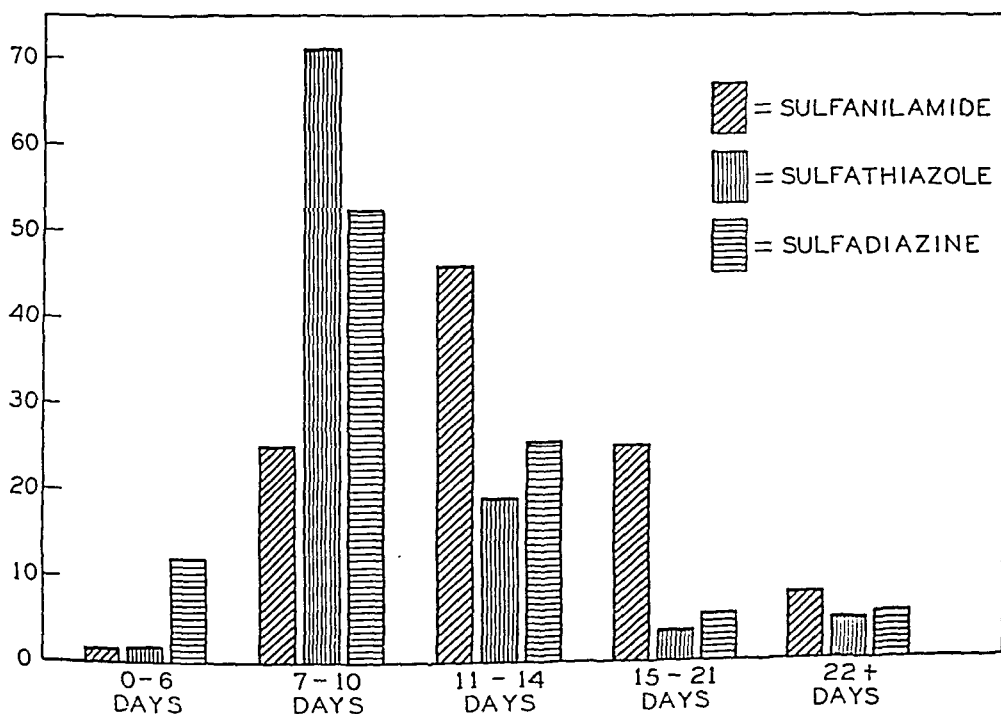


Fig. 6.—Days of hospitalization.

Fig. 7 illustrates various differences in the daily and total dosage employed, the duration of treatment in days and correlates the incidence of recurrence of the disease and the failure with each of these factors. It is seen that wide variations in the therapeutic methods were utilized. The daily dosage varied from 2 to 7 Gm., the total dosage from 7 to 73 Gm., and the number of days of treatment from 1 to 13. The instances of prolonged and high dosage were in patients with unusual circumstances or for experimental reasons, and were few in number. The most commonly employed daily dose was 5.4 Gm. with sulfanilamide, 6.0 Gm. with sulfathiazole and 4 Gm. with sulfadiazine. The most frequently used total dosage was between 36 and 40 Gm. for sulfanilamide and sulfathiazole, and 20 and 29 Gm. for sulfadiazine. The treat-

ment was continued somewhat longer in the sulfanilamide group than in the other groups. During the progress of the study we gradually employed both a smaller daily and total dosage and in addition, the duration of treatment tended to be of shorter duration. A careful survey of this chart shows that the majority of the patients that subsequently developed a recurrence of the disease, were treated with a relatively large dosage over a satisfactory period of time. In fact, the recurrences are distributed from a statistical analysis according to chance, and none of the data indicates that recurrence of disease was in any way dependent upon any particular plan of therapy. In addition, two-thirds (18) of those that developed a recurrence, later freely admitted the possibility of reinfection. Of the remaining 9 we have good reason to believe that reinfection was possible in some instances.

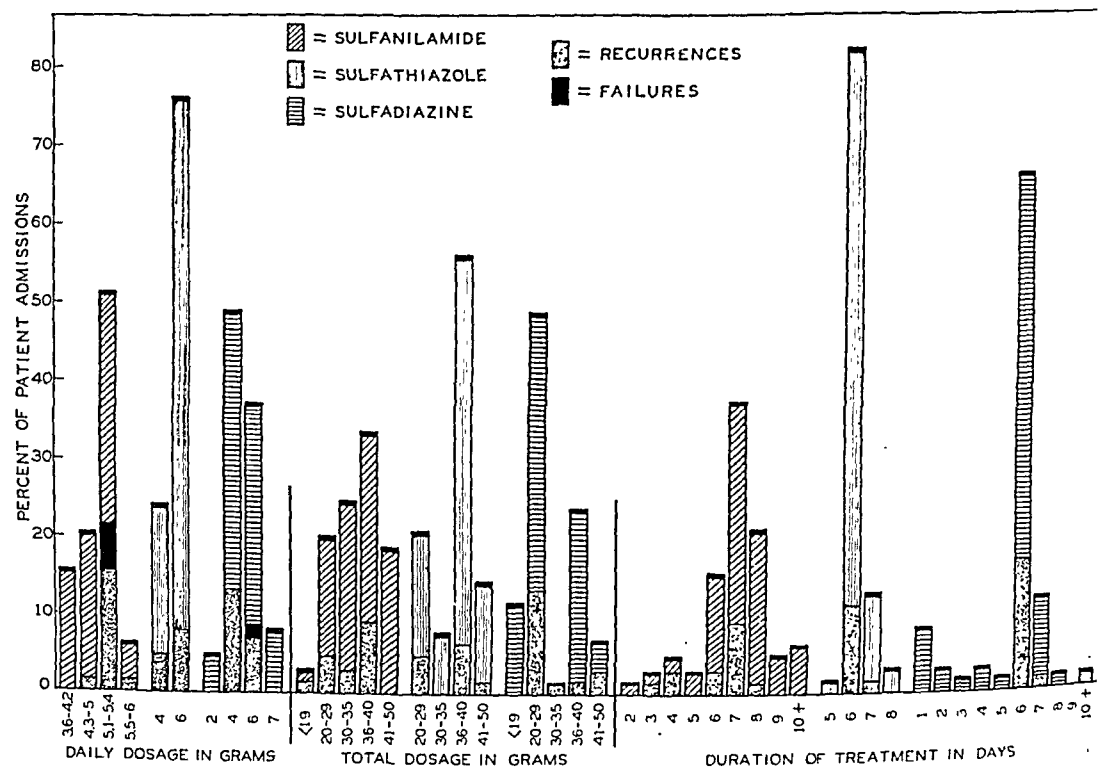


Fig. 7.—Treatment. Daily dosage, total dosage, and duration correlated with recurrence of disease and failures.

On the other hand, in one patient, at least, we feel that reinfection was most unlikely and this recurrence would seem to represent a genuine exacerbation. The patients in the four instances of sulfanilamide failure all received 5.4 Gm. of the drug per day. We feel, at the present time, that if evidence of a satisfactory result is not evident within forty-eight hours, there is little use in continuing the drug in question.

In order to evaluate the specificity of the various compounds we started taking smears and cultures after the lapse of several days. As the sulfanilamide study progressed we shortened this interval in turn, because the first specimen studied was frequently negative, to 48, 24, and 12 hours, respectively. Following the introduction of sulfathiazole

and sulfadiazine, the interval was shortened further so that a considerable number of studies on the secretions were obtained at intervals of two hours after the onset of treatment. The blocks in Fig. 8 illustrate the interval from the onset of treatment to the time of the *first* examination of the secretions. In many instances subsequent studies were carried out at frequent intervals, but this information is not included on the chart. Earlier statements explain why there were not as many observations made early in the sulfanilamide group as there were in the other two groups. The curve on this chart shows the number

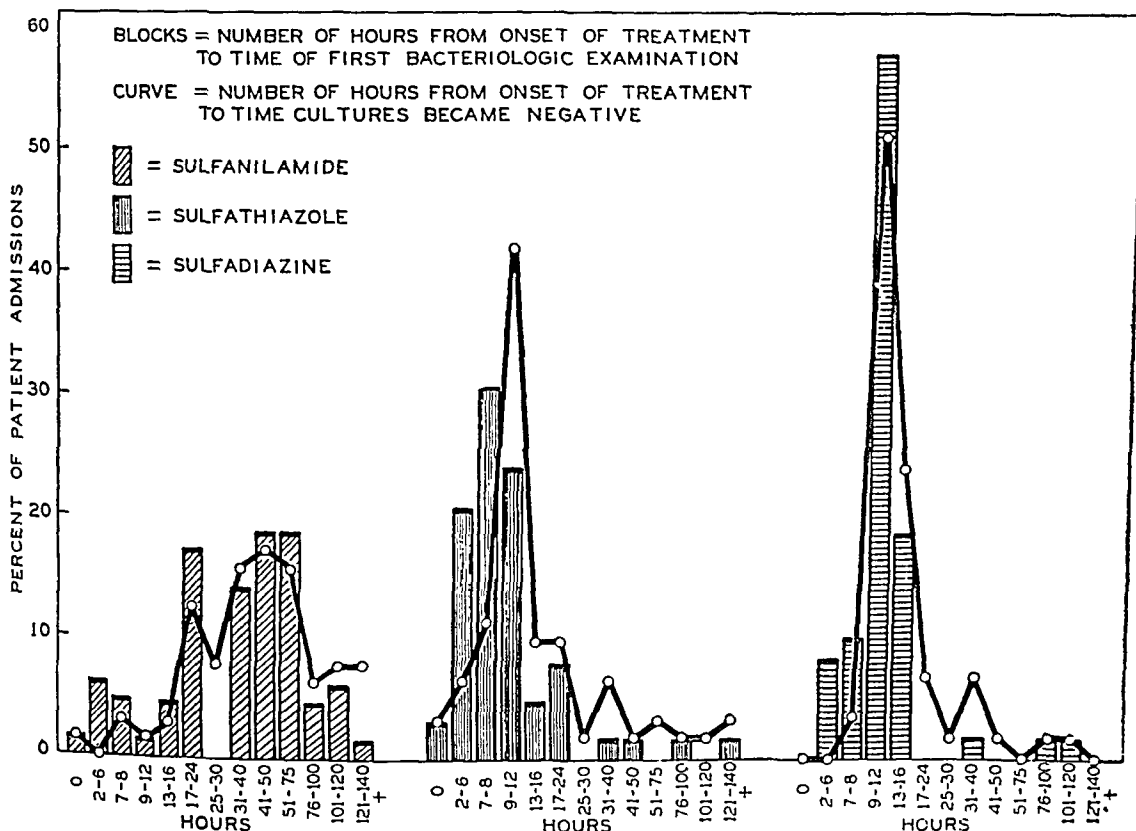


Fig. 8.—Results of treatment.

of hours from the onset of treatment to the time the smears and cultures became negative. Bacteriologic cure is thus seen to be evident most frequently in the sulfanilamide group in forty-one to fifty hours and in the sulfathiazole and sulfadiazine groups in nine to twelve hours. Consideration of the data expressed by the curve does not give all desired information because on many occasions the first specimen studied was negative. Obviously then, under those circumstances the exact time of bacteriologic cure was unknown.

For more positive information, Fig. 9 was constructed and illustrates the length of time from the onset of the treatment to the time of the *last* known positive culture. Fifty-nine patients had positive laboratory



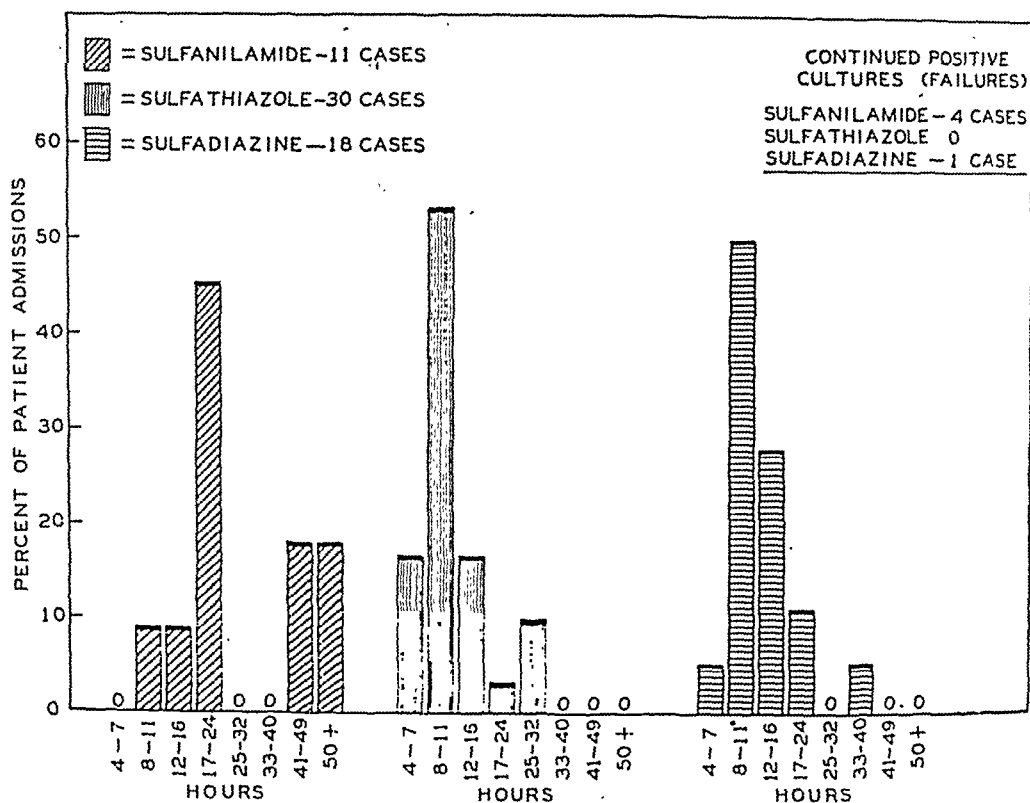


Fig. 9.—Results of treatment. Known positive cultures after onset of treatment.

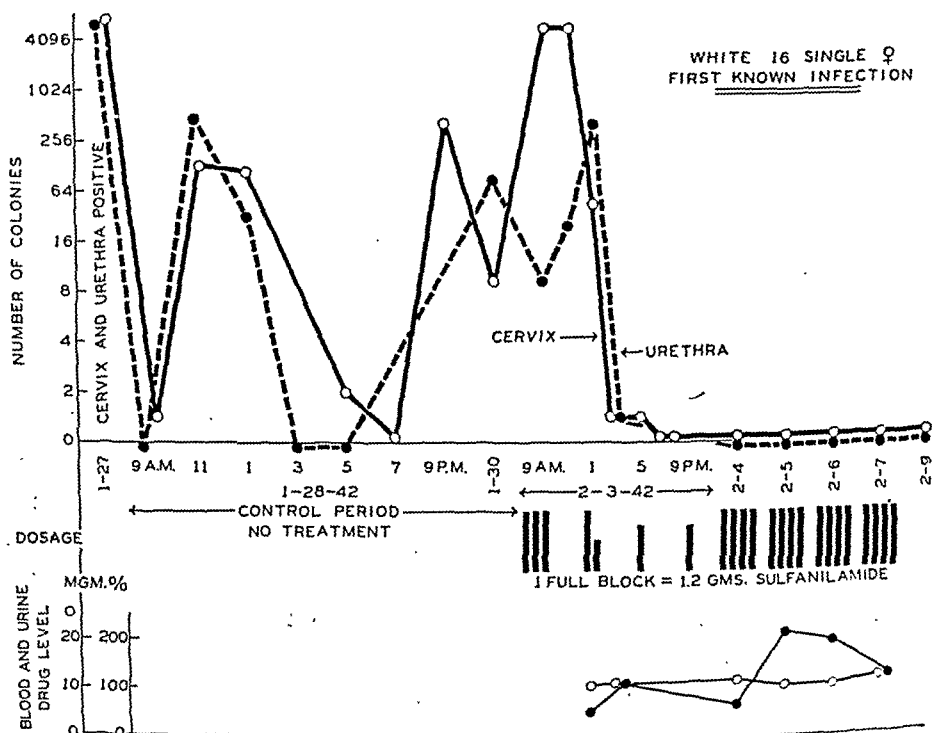


Fig. 10.—Acute gonorrhea treated with sulfanilamide.

tests following the onset of treatment. Eight patients in the sulfanilamide group, 3 of the sulfathiazole group, and 2 of the sulfadiazine group had positive cultures more than twenty-four hours after the onset of treatment. Furthermore, 6 of the sulfanilamide treated cases had positive cultures more than fifty hours after the onset of treatment.

Fig. 10 illustrates graphically the sequence of events in a patient treated with sulfanilamide with reference to gonococcus colony counts on standard unit volumes of secretion obtained from the cervix and the urethra. The number of colonies are represented by figures in a geometrical progression, 4,096 representing infinity as far as quantitative determinations are possible. After the diagnosis was made 7 cultures were obtained at two-hour intervals when no medication was administered, to serve as a control of the effect of repeated cultures on colony counts. Six days later cultures were obtained at the same intervals.

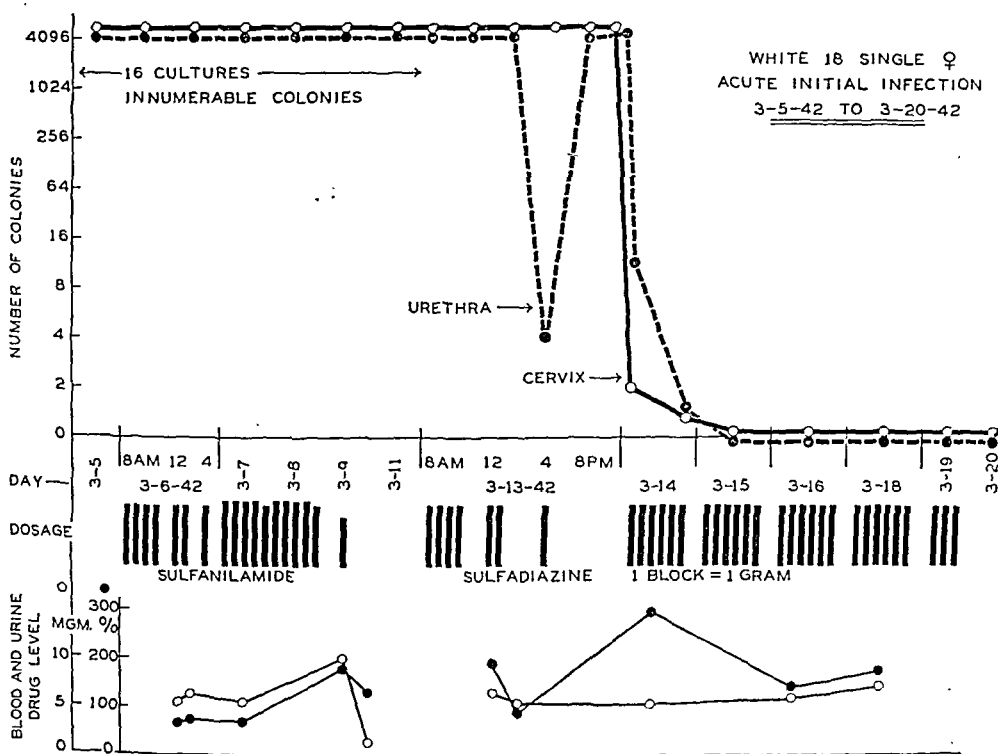


Fig. 11.—Acute gonorrhea treated with sulfanilamide and sulfadiazine.

Sulfanilamide (3.6 Gm.) was administered at the time the first culture was taken and 1.8 Gm. four hours later followed by 0.9 Gm. every four hours thereafter. The colony counts indicate a sudden diminution in the number of gonococcus colonies and the cultures became negative in ten hours. This patient was one of two, in the sulfanilamide group, who developed a bacteriologic cure within such a short period of time. The blood concentration was 11 mg. per cent within four hours after the onset of treatment where it remained remarkably constant until the drug was discontinued five days later.

Fig. 11 is constructed along similar lines, expecting no control period is included. The patient was a single, white girl with what was thought to be an acute initial infection confined to the lower genitourinary tract.

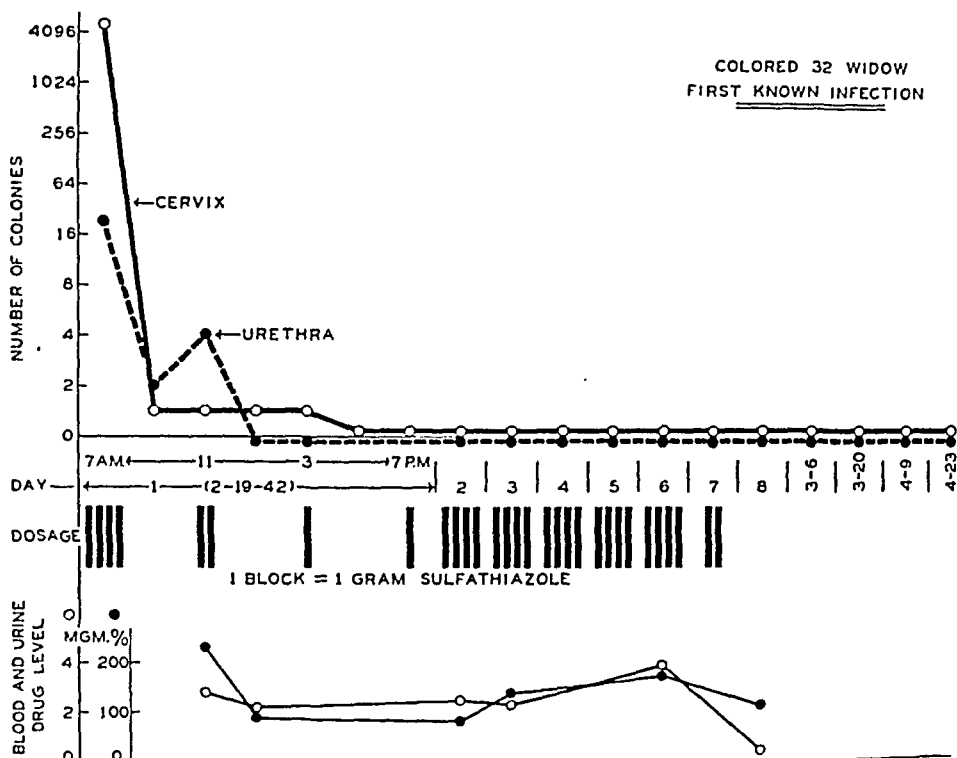


Fig. 12.—Acute gonorrhea treated with sulfathiazole.

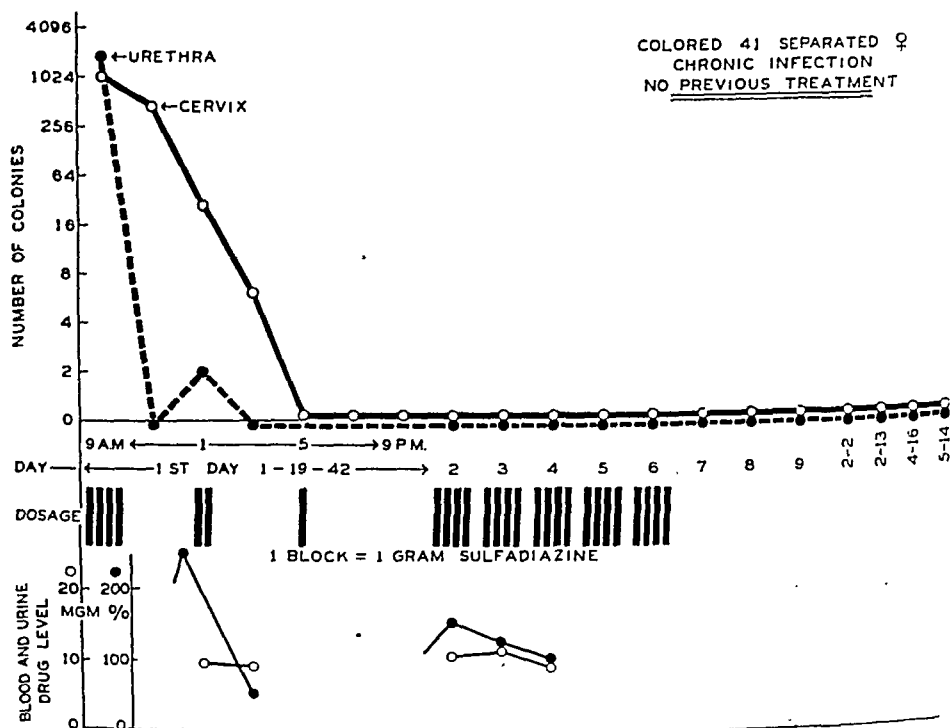


Fig. 13.—Chronic gonorrhea treated with sulfadiazine.

husband discontinued eating above-mentioned articles of diet, and the patient had no further headaches.

It is hoped that this report will stimulate further work to determine the answer to several questions:

1. Would female blood of the same group as the husband's be equally effective?
2. Would male or female blood from persons of other groups be effective?
3. Would serum or plasma of proper group but other than that of the husband produce the same result?
4. Is the active agent some hitherto unknown factor other than blood (or tissue?) group incompatibility?
5. What was the constituent of the husband's blood that caused the allergic headache in the patient after intramuscular injection of his blood when he had taken any food to which she was sensitive (histamine?)?

If female blood would relieve the patient, it would be proof that male hormone could not be a factor. If male blood of the woman's own blood group would produce the result, it could not be the specific blood group incompatibility which was the underlying cause of the distress in the pregnant woman.

The work of W. Haase<sup>2</sup> has shown that incompatible blood grouping had nothing to do with the development of eclampsia, since the blood groups of the mother, father and baby were all the same in a series of 20 unselected cases of eclampsia.

It is worthy of note that Polayes<sup>30</sup> also investigating eclampsia found that in a series of 12 cases the mother and baby were uniformly of the same blood group. The results of these two separate investigators suggest that the blood grouping may have had something to do with the development of eclampsia but the exact mechanism of the production of the toxemia is unknown. It could not have been due to A or B antigen incompatibility but to some intra-group reaction.

Since this report was first prepared, a number of obstetricians have been contacted. One tried injections of the husband's blood on four patients suffering from hyperemesis. In all of these cases the hyperemesis was controlled by the use of three or four intramuscular injections of the husband's blood. The final work on the antigen factors is still to be carried out in some cases. In some the mother was not a universal donor as in the case above reported.

It is recognized that many other methods of treatment have been reported and are effective in many cases. Some of these were tried in previous pregnancies in the above-mentioned patient, such as proluton,<sup>3</sup> intravenous glucose and insulin,<sup>4, 5</sup> autohemotherapy,<sup>6, 7</sup> various vitamins,<sup>8</sup> calcium therapy,<sup>9</sup> and wheat germ oil. Other methods advocated by various authors are variations of hormone therapy,<sup>10</sup> adrenal cortex,<sup>11, 12</sup> liver injections,<sup>13, 14, 19</sup> various vitamin injections,<sup>12, 15-19</sup> enemas of the patient's urine,<sup>20, 21</sup> psychotherapy,<sup>22</sup> adjustment of the salt balance,<sup>23</sup> administration of fibrinolysate,<sup>24</sup> histidine,<sup>25</sup> amyl-nitrate and glyceryl-trinitrate,<sup>26</sup> biliary drainage with duodenal tube,<sup>27</sup> Chinese acupuncture,<sup>28</sup> parathyroid extract with calcium,<sup>9</sup> phenobarbital, pneumoperitoneum.<sup>29</sup> The use of husband's blood was mentioned but not discussed in articles by LeFevre,<sup>5</sup> Saxon and Stoll<sup>6</sup> and also reported on by Thierry,<sup>31</sup> who used serum in five cases, Canouet<sup>32</sup> and W. S. Horn.<sup>33</sup> Treatment by injections of husband's

others were performed after the cessation of administration of the compound and, accordingly, an average of the levels is not particularly illuminating. For this reason, we have plotted in this chart an average of the highest blood levels obtained, in milligrams per cent, for different dosages of the three drugs. In general, it appears that the smaller doses are more efficiently utilized at least as far as availability in an uncombined form is concerned. From a careful review of all of our material we feel that, if necessary, blood and urine determinations could be dispensed with, provided the daily dosage is small (4 Gm. or less), the duration of treatment is short (not over five or six days) and an adequate urinary output is maintained.

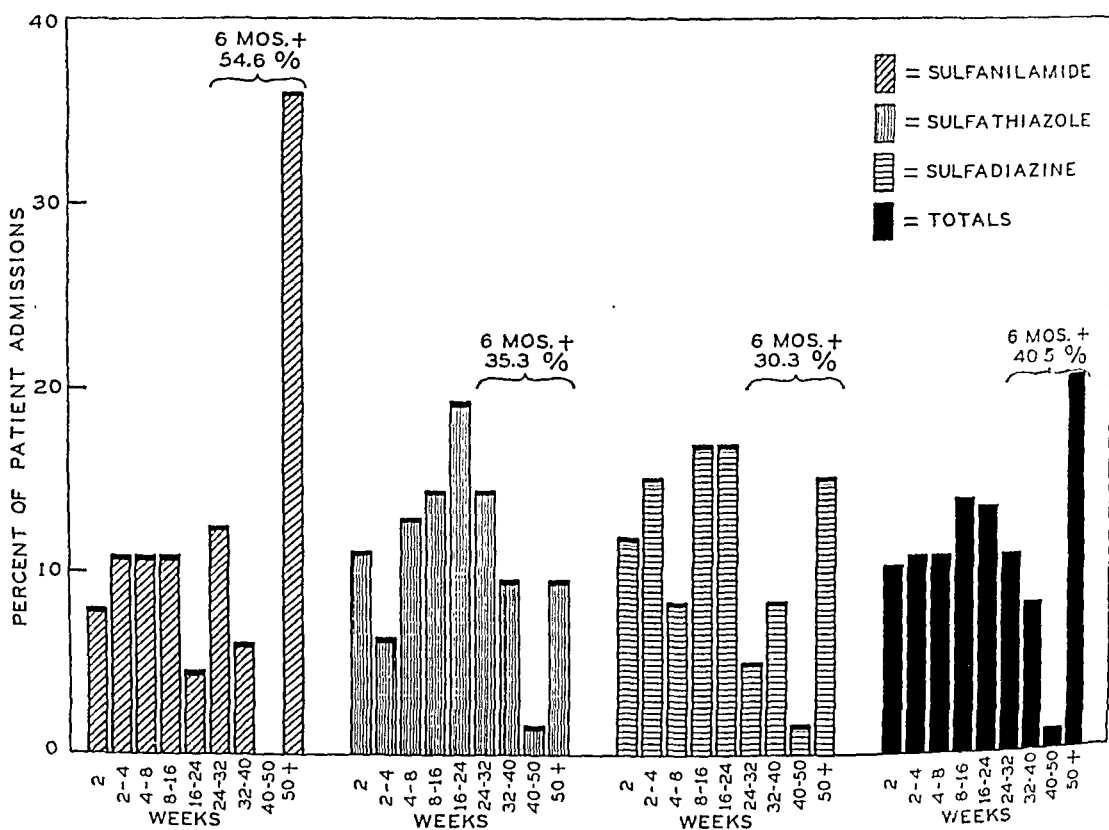


Fig. 15.—Period of follow-up observation.

We have made every effort to obtain a satisfactory period of observation in a special follow-up clinic. Fig. 15 summarizes the length of this interval. Many of the patients are still being observed. However, as of April last it is seen that slightly over 20 per cent were not followed for more than one month, 25 per cent were followed from one to four months while an almost equal number were observed from four to eight months. Slightly more than 20 per cent were kept under observation for one year or longer. In the patients that had recurrence of the disease later the period of follow-up is calculated only to the time of the recurrence. This means the actual period of observation is somewhat longer than is illustrated in this chart. The average number of examinations in the hospital following the onset of treatment was 7.9 and in the follow-up clinic after discharge 3.1 per patient.

The complete lack of response to the sulfanilamide, however, serves as an adequate control. Many of the infinite colony counts are excluded from the graph because of their similarity. Four days after discontinuing the sulfanilamide, sulfadiazine was started and the same observations made. Cultures thirty-six hours later were still positive which, with the exception of one failure, represents the slowest bacteriologic response observed with this medication. Drug concentrations in the blood were a little lower than usual but we do not believe this factor offers a satisfactory reason for the failure of the sulfanilamide or the slow action of the sulfadiazine.

Fig. 12 represents the course of a 32-year-old widow with a first known infection treated with sulfathiazole. Blood concentrations are lower which is characteristic of this drug. A bacteriologic cure, however, was obtained in ten hours and a significant decrease in the colony count was noted two hours after starting treatment.

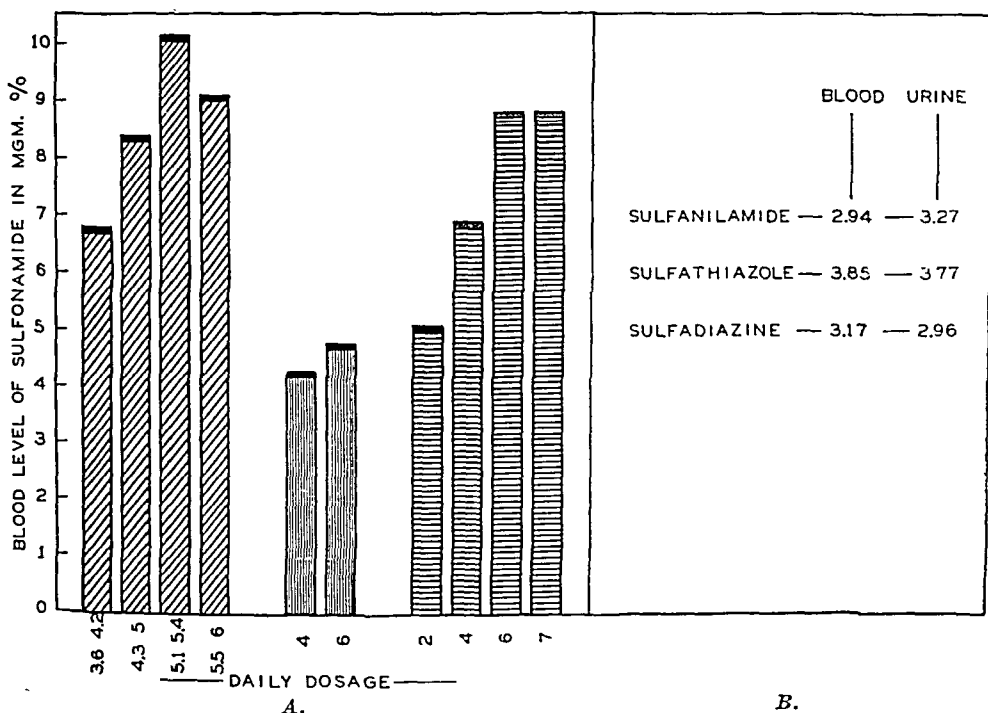


Fig. 14.—A, Average highest blood levels of sulfonamide in milligram per cent correlated with daily dosage. B, Average number of blood and urine sulfonamide determinations per patient.

Fig. 13 is that of a 41-year-old separated, colored woman with a chronic infection. A bacteriologic cure was established in eight hours following the administration of sulfadiazine. The blood level was 9.6 mg. per cent within four hours after the onset of treatment and was well maintained on a 4 Gm. daily dose. Cultures and smears taken at regular intervals have all been negative and the patient is still under observation.

Fig. 14 illustrates the average number of sulfonamide determinations in the blood and urine in the three groups. The data are based on a total of 591 blood and 441 urine studies. A considerable number of the patients had daily tests performed, while in others tests were done every second or third day during the period of therapy. Many of the tests were carried out before a sulfonamide equilibrium was established while

developed a moderate hemolytic anemia. No such changes were noted in the sulfathiazole or sulfadiazine groups. No significant change in the white cells was noted. Extensive experimental physiologic and pathologic investigations on possible renal lesions following the administration of sulfathiazole and sulfadiazine are being conducted by different workers at the present time. It appears that definite toxic changes not infrequently occur in the kidney of the dog following the administration of sulfadiazine. There is no evidence, however, that such changes take place in man in the dosages referred to and in the presence of good kidney function. There has been no instance of microscopic or gross hematuria nor renal colic such as has been reported by some authors during the administration of sulfadiazine or sulfathiazole. We have not been able to detect any suggestion of renal changes in our patients in this series, and it is our opinion that in the dosage employed, in the absence of any pre-existing renal lesion and if an adequate urinary output is maintained, no real danger exists.

#### DISCUSSION

It has been difficult to subject our clinical observations to statistical methods of analysis. Leucorrhea and the acute evidence of inflammation in the lower genitourinary tract often subside rapidly. However, where there is a mixed infection at these sites some chronic discharge may persist. It is our impression that acute gonorrheal salpingitis subsides and is cured just as rapidly as is the process in the lower genital tract. It must be made clear, however, that chronic pelvic inflammatory disease and tuboovarian masses caused by other microorganisms are not, in our opinion, affected to even the slightest degree by any of the sulfonamides referred to.

Recently we have been studying the sulfonamide concentration in the cervical secretions for some clue as to why such dramatic results are obtained. Our findings to date indicate much lower concentrations of both sulfathiazole and sulfadiazine than is present in the blood.

Spread of the disease from the lower to the upper genital tract occurred on only two occasions during or following treatment. Both of these patients are included in the failures.

All of our data indicate that sulfanilamide is less specific and slower acting than either sulfathiazole or sulfadiazine. In addition to the previously presented data, we have had the opportunity of observing the results of administering 3.6 Gm. or less per day of sulfanilamide to a few ambulatory patients. The persistence of positive cultures in these cases lends support to the above statement. Another disadvantage to this compound lies in the frequency with which it causes disturbing subjective symptoms. Sulfathiazole and sulfadiazine are almost equally specific. Sulfadiazine is slightly more rapid in its action and causes fewer subjective symptoms.

Fig. 16 presents in summary the end results. The gonorrheal infection was eliminated from both a clinical and bacteriologic point of view in 180 out of the total of 185 admissions of 158 patients. Five drug failures were observed, 4 being in the sulfanilamide and one in the sulfadiazine group. Three of the sulfanilamide failures promptly responded to one of the other sulfonamides while the other case occurred before these compounds were available and that patient was retained in the hospital until a spontaneous cure developed. The sulfadiazine failure later responded to a second course of the same drug during the puerperium. In 27 instances, there was a later recurrence of the disease. Approximately one-half of these occurred more than four months after treatment. In two-thirds of this group, the possibility of reinfection

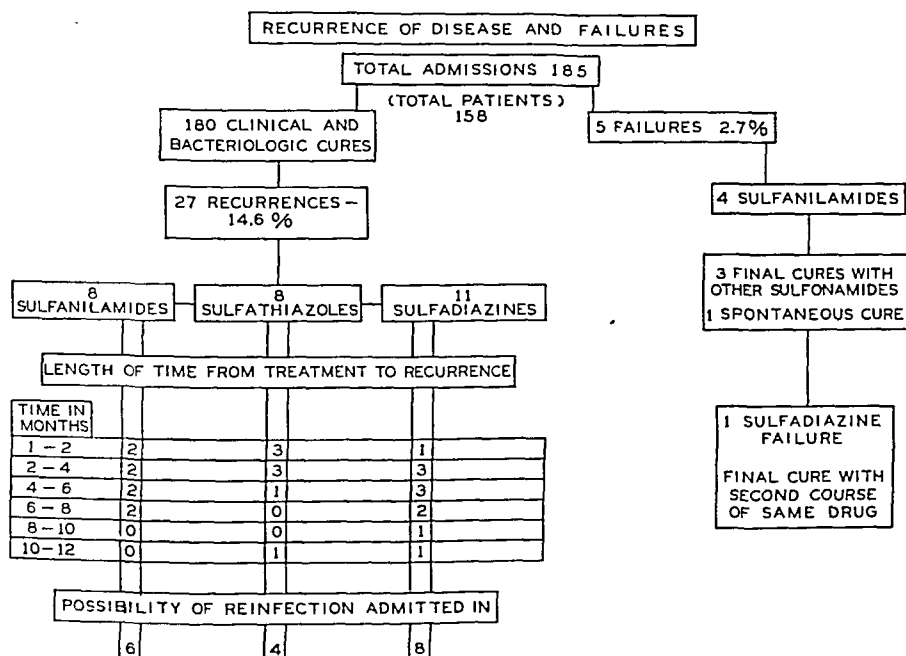


Fig. 16.—Summary of end results.

was admitted, while in the remainder such an admission was not obtained. Obviously, it is impossible for us to say with certainty whether these infections represent an exacerbation of the original infection or whether they are reinfections. Our own feeling, however, is that the great majority at least are new infections.

#### TOXICITY OF THE DRUGS

Two-thirds of the sulfanilamide group had toxic manifestations, such as nausea, vomiting, anorexia, cyanosis, chills, fever, vertigo, headache, etc., while only 7 of the sulfathiazole and none of the sulfadiazine groups had such findings. Hemoglobin determinations, red and white blood counts, and sedimentation rates were routinely performed at frequent intervals on all patients. The only significant change noted on an analysis of these data was the tendency to develop anemia during sulfanilamide administration. In fact, two patients in this series actually



6. Bacteriologic cure is most frequently encountered within nine to twelve hours after the administration of sulfathiazole or sulfadiazine and forty to fifty hours after sulfanilamide.

7. Four grams of sulfadiazine or sulfathiazole in divided daily doses for six consecutive days constitutes, at the present time, the most ideal form of therapy.

8. Bacteriologic cures were established in 180 out of 185 admissions of 158 female patients with gonorrhea. There were 27 recurrences of the disease which were thought, for the most part, to be new infections. There were four failures with sulfanilamide and one with sulfadiazine.

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#### DISCUSSION

DR. FREDERICK H. FALLS, CHICAGO, ILL.—The use of any agent in the cure of disease must always be evaluated in the light of what may be expected to happen if the disease were allowed to progress untreated or treated by some other method. Dr. Douglas has rightfully pointed out that gonorrhea in the female generative tract is rarely if ever fatal; that a large percentage of the cases are infections of the lower genital tract which tend to die out spontaneously. It is a matter of common knowledge that the same rule holds true for infections of the upper genital tract. The true worth therefore of a given method of treatment for such a disease depends upon the speed with which the results are accomplished, their permanence, and on the innocuousness of the remedy.

The vulnerability of the gonococcus to various therapeutic agents is well recognized, and one must remember that specific fever therapy in this disease antedated Carpenter's work by many years. Vaccines, composed of dead gonococci and mixed bacterial filtrates known as "phylacogen" were used freely as early as 1910. This was followed by milk injections, then the Elliott treatment and more recently by the Newman thermo-flo, all of which have depended on raising the temperature of the tissues to devitalize the gonococcus. Each of these methods produced good results according to their sponsors, but all lack the dramatic speed in attaining a cure reported by the method here under discussion.

I should like to raise the question of the diagnosis of gonorrhea in the female based on the finding of a gram-negative diplococcus by culture from the urethra and cervix. Would we make a diagnosis of pneumonia if we could cultivate the pneumococcus from the nose and throat, or of diphtheria if we found a gram-positive rod that grew well on Loeffler's media in the throat? Should we call every one a typhoid fever patient from whom a typhoid-like bacillus may be cultivated from the stool? I should be in favor of disregarding for the purpose of a study of this kind all cases which did not present a definite history or clinical symptoms or indisputable stigmas of gonorrhea. Not that I would minimize the important implications of this study in demonstrating a larger number of cases which ap-

Occasionally in the control of treatment, smears revealed extracellular gonococci but cultures inoculated from the same exudate failed to grow. Careful investigation of this phenomenon leads us to believe that such forms are nonviable. We have frequently used media for culture containing para-amino-benzoic acid (5 mg. per cent), to inhibit the action of any sulfonamide carried by the inoculum to the media. The results were the same as that obtained were this inhibitor not added. The explanation may be that the exudate actually contains para-amino-benzoic acid, which is very likely so, or that the concentration of the sulfonamide is so weak that it has no effect.

All of our observations indicate that a satisfactory therapeutic response is obtained promptly or not at all. If negative cultures are not obtained within forty-eight hours after the onset of treatment it would appear that there is little use in continuing the treatment, at least with the particular sulfonamide concerned.

Four grams of sulfathiazole or sulfadiazine daily gives just as satisfactory results as does the 6 Gm. daily dosage and, in fact, our most recent but somewhat limited experience indicates that a 2 Gm. daily dose may be often equally efficacious. However, this is not always true and, accordingly, we cannot advise its routine use as has been suggested by many public health agencies. Equally good results were obtained in the cases where 1 Gm. of the drug was given at hourly intervals for seven hours and then the drug entirely discontinued. In the light of these observations, a rational plan of treatment might be 4 Gm. per day in divided doses of either of these compounds for six days. If it were necessary to supervise the administration of the drug, 1 Gm. could be administered every hour for 7 doses. In some respects this latter plan appears more logical than the former but, as yet, we have not had sufficient experience to recommend its general use.

#### CONCLUSIONS

1. Cultures of cervical, urethral, or other exudates are much superior to reliance on smears alone for the diagnosis, control of treatment, or follow-up observations in the management of patients with gonorrhea.
2. The latent form of the disease is often asymptomatic or associated with leucorrhea only (43 per cent of cases) and, very frequently, cannot be recognized without the aid of cultures.
3. The efficacy of the therapy is unaffected by age, color, pregnancy, duration of disease, or site of infection.
4. Treatment and its control is more efficient if the patient is hospitalized.
5. Of the three drugs employed sulfanilamide is the least specific and the most toxic. Sulfathiazole and sulfadiazine are much more specific and rapid in their action and definitely less toxic. Sulfadiazine appears to be slightly more efficient than sulfathiazole and is the least toxic.

two menstrual periods with negative smears and cultures before they are pronounced cured.

Sulfanilamide should not be used in children, partly because of its toxicity and also because in children it tends to produce drug-fast strains. Sulfathiazole appears to be the drug of choice in the treatment of children, although we have not treated a sufficient number to draw final conclusions. In some instances in children, we supplemented sulfonamide therapy with stilbestrol in order to obtain a cure.

The sulfathiazole and sulfadiazine are the drugs of choice in the treatment of women. The rate of cure with sulfadiazine was 95.8 per cent. The women respond rapidly to the sulfonamides and become noncontagious earlier than when local treatment is used. Secondary complications are rare when the sulfonamide therapy is administered early. Drug-fast strains were noted in only 1 in 354 patients.

DR. CHARLES C. NORRIS, PHILADELPHIA, PA.—In the gonorrhea clinic at the University of Pennsylvania 158 cases, almost all of whom are adults, have been treated with sulfathiazole during the past year. Eighty per cent of these cases were in the chronic stage. One of our outstanding conclusions is that very little can be determined by clinical diagnosis in the chronic cases. So many women have suggestive signs who do not prove to have gonorrhea culturally, while so many positive cases occur in which the stigmas are inconclusive or absent. We concluded also that cultures were twice as reliable as other methods, including smears.

Nearly all of our cases were studied for three months. We had about the same number of negative cultures within the first week as has been reported. In the cases that were studied for three months, however, we had 17 per cent of recurrences and of this number the large majority were cleared up by the second course of treatment. However, there were a few cases among that group which seemed to be very difficult and did not respond to a second course of treatment. Of course, those cases may possibly be due to reinfection which is not admitted by the patients. We had few reactions. Treatment with sulfathiazole is the best method of treating gonorrhea in the lower genital tract of women, and I believe has some value in the treatment of gonococcal pelvic inflammatory disease.

DR. GEORGE W. KOSMAK, NEW YORK, N. Y.—I believe that this subject must be looked at from another point of view than the purely clinical one and that we should give some attention to the public health aspects in question. In that connection I do not believe that we should accept without some question the entirely enthusiastic reports which have been brought forward with respect to the treatment of gonorrhea by the sulfa group of drugs. These enthusiastic reports have led in one instance that I know of, and there may be others, to the publicity by public health agencies about the unfailing value of the sulfanilamide group in the treatment of gonorrheal infection. In fact, in the particular instance of which I speak, a certain department of health was ready to post in public conveyances a notice to the effect that gonorrhea could be cured by sulfathiazole, and the group backing this proposition went so far as desirous of publicizing the fact that the public should be informed about the value of these drugs to the same degree that they have been already informed about the value of quinine in the treatment of malaria. In other words, that any person suspecting they have an infection or having been told that they have a gonorrheal infection, might go to any corner drugstore and buy a box of sulfathiazole tablets for self administration.

Our Society, to which this excellent study has been presented, need not perhaps pay much attention to the matter. However, the outcome of such presentations may be that, getting into the hands of public health officers and others who are concerned with the reduction of these venereal diseases, the resultant effect may prove unfortunate. I do not believe that it is desirable for the public at large to

parently are gonorrheal carriers, but to say that by a certain method we have cured these women of gonorrhea is hardly justifiable.

The second question I would raise is whether the evidence here presented definitely settles the question of cure in a great group of these patients. It certainly shows that when the sulfa content of the blood is raised to a certain level that some of the drug appears in the cervical and urethral secretions and that under these circumstances the organisms previously cultivated from these surfaces could no longer be made to grow. It would seem that the organism might be inhibited from growing by the drug without being killed, and that unless all of these cases were followed up by culture, after all therapy had been stopped and the blood level of sulfathiazole had returned to normal, that the possibility of revival of the organism under the more favorable conditions might be expected. This might account for some of the recurrences here cited as potential reinfections. It would also have been more convincing if all of the gram-negative diplococci isolated by culture had been subcultured and their carbohydrate fermentation reactions studied in order to prove their right to be designated gonococci.

The susceptibility of this organism to sulfa drugs can be shown by an accidental circumstance which occurred a few weeks ago at the University of Illinois. A class in bacteriology was given some human blood to make up blood agar plates. The plates were inoculated with live cultures but no growth obtained on incubations. Subsequent investigation showed that the blood had been taken from a patient who was under treatment with a sulfa drug.

The results of the study of 100 cases of acute salpingitis at Cook County Hospital with a comparison of patients treated with sulfanilamide, and those not receiving the drug are as follows:

Patients receiving sulfanilamide:

|                             |            |
|-----------------------------|------------|
| Average stay in hospital    | 11.23 days |
| Average days of temperature | 6.64 days  |
| Average time sick           | 17.83 days |

Patients *not* receiving sulfa drugs:

|                             |            |
|-----------------------------|------------|
| Average stay in hospital    | 11.03 days |
| Average days of temperature | 6.80 days  |
| Average time sick           | 20.48 days |

The patients with the sulfa drug received at least 240 gr. while being treated. The highest amount given was 1,200 gr. while being treated.

DR. FRED L. ADAIR, CHICAGO, ILL.—For a number of years past Dr. Hessel-tine, Dr. Lucile Hac, and I have been studying patients, principally ambulatory, secured through the Social Hygiene Clinic in Chicago. Naturally the patients did not report unless they had some symptoms. We were unable to follow them closely within a few hours after treatment. I think, however, we can draw some conclusions from this series of over 480 women and some children who were treated.

With the different sulfa drugs, we have in the main drawn about the same conclusions as Dr. Douglas. Certain differences in the blood level of these drugs may be obtained in relation to the dosage. For instance, with the sulfathiazole we had a blood level of 2 to 3 mg. per cent; with sulfadiazine we had a level of 4 to 6 mg. per cent, and with an increased dosage of the sulfadiazine we had as high as 11 mg. per cent with 3 Gm. doses.

We rely much more on cultures than we do on smears for diagnosis as well as for the criterion of cure. With sulfadiazine, we had 98 per cent negative cultures within four days; with sulfathiazole, we had 97 per cent; with sulfapyridine, 93 per cent; and with sulfanilamide, 88 per cent negative cultures.

As a criterion of cure we have used the silver nitrate method, but we have found that menstruation is probably the best provocative test. We run our cases through

# STUDIES OF THE HUMAN CORPUS LUTEUM\*

## EVIDENCE FOR THE EARLY ONSET OF REGRESSION OF THE CORPUS LUTEUM OF MENSTRUATION

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THE subject of this report is concerned with the time at which regression begins in the corpus luteum of menstruation.

The life cycle of the corpus luteum of menstruation in the human being has been described and its division into four typical stages has been universally accepted. These stages are termed proliferation, vascularization, mature or blossom stage, and stage of regression (Meyer, 1911; Frank, 1914). Meyer (1911 and 1932) observed that the blossom and regression stages were imperfectly limited and stated that the beginning of regression could not be definitely recognized. Novak (1934 and 1941) stated that regression begins shortly before the onset of menstruation, about the twenty-sixth day in a patient with a twenty-eight-day ovulatory cycle. The material to be presented here indicates rather that regression begins at the termination of the so-called vascularization stage, four to six days before the onset of menstruation.

In order to avoid confusion, I wish to state that I shall not describe the reported specimens in relation to days of the menstrual cycle. The variability in the length of normal cycles is so great that the dating of specimens according to this method may lead to confusion. Since that portion of the menstrual cycle between the time of ovulation and the onset of menstruation is relatively constant, I shall date all specimens by the probable days of age of the corpus luteum. Exact age of a given corpus luteum is difficult to determine. Histologic characteristics offer the best method. It is possible to evaluate the approximate age within two to three days by these histologic characteristics. For the most exact age determinations, it is necessary to study a series of specimens in this report. By this method of comparison the age of an individual specimen can be estimated more accurately. The study of the normal endometrium is also an aid in making age determinations of corpora lutea.

### MATERIAL AND METHODS

The 97 specimens studied were obtained from patients undergoing pelvic operations by members of the gynecologic department of St. Luke's Hospital, to whom I express my appreciation. The patients were in active menstrual life and the menstrual cycles were normal. The

\*Read, by invitation, at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.

be told that gonorrhea is an easily curable disease, whether in men or women. I am afraid that such an attitude might contribute to the further dissemination of a disease which now constitutes a menace to our Armed and Defense Forces. In the present war emergency every effort is being made to reduce the incidence of venereal disease. I do not feel that it would be desirable that people should be misled by the claim that gonorrhea can be cured easily and without satisfactory medical oversight and control.

DR. DOUGLAS (closing).—In discussing this subject we must clearly differentiate chronic pelvic infections with associated inflammatory masses from gonorrhea. The former condition is not in our experience favorably affected by any of the sulfonamides that have been employed. On the other hand, if a therapeutic response is not obtained in the treatment of gonorrhea within forty-eight hours, consideration should be given to changing the compound or stopping its administration.

Reference has been made to the production of an asymptomatic carrier state. We have encountered this phenomenon with the smaller dosages of sulfanilamide but to the best of our knowledge we have not encountered the condition following the administration of sulfathiazole or sulfadiazine. However, we believe this possibility is one reason why the daily dosage should not be too low.

Dr. Falls has referred to heat therapy. The treatment introduced by Carpenter was based on the thermal death time of the infecting strain of gonococcus. In order for a cure to follow, the body temperature should be raised to 41.5° C. as long or longer than this period of time. Other forms of heat treatment where this temperature is not reached or maintained for the indicated time does not constitute specific fever therapy as I have employed the term.

The question has been raised regarding the identification of the strains isolated. Sugar fermentation reactions were frequently employed and the oxidase reagent was routinely used. The asymptomatic patients referred to were sent to us for treatment by the Department of Health of New York City. They had already disseminated the disease.

I may say that the time required for the cultures to become negative after the onset of treatment has been the subject of thorough investigation. We have employed p-amino-benzoic acid in our media to nullify the effect of any sulfonamide carried in the secretions to the media. Determination of the concentration of the drug in the cervical secretions has also been carried out on many occasions. As a result of these studies we are forced to conclude that the reported results are correct. It may be that this form of treatment is more specific in the female than in the male.

Public Health agencies already have the information and are widely disseminating it. In many instances they advocate a 2 Gm. daily dosage which we believe to be effective usually, although not always. For this reason we believe the 4 Gm. daily dosage more desirable.

We would prefer to be less enthusiastic but our results hardly justify such a position. The term "cure" as employed is modified by "bacteriologic" when based on laboratory data and "apparent" when determined by clinical findings.

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blood is not mentioned in any of the recent textbooks on obstetrics although Kosmak,<sup>37</sup> in 1922, made reference to a report by Blair Bell, the original reference for which the author was unable to find.

*Additional Comment.*—It is interesting to note that the baby, now nine months of age, is extremely sensitive to cow's milk. She became pulseless, cyanotic, and went into shock when given her first tablespoonful of cow's milk at seven months of age. The reaction was repeated on a second trial of a smaller amount of cow's milk one month later.

It would seem very definite that since many other forms of treatment had been tried in 7 pregnancies that the injections of husband's blood had a decidedly advantageous therapeutic effect in this case and in other cases in which it has been tried. Although the cause of the hyperemesis and the reason for the immediate relief of symptoms are still conjectural, the fact remains that all the symptoms ceased with this simple treatment. The patient was allergic to certain foods and the baby has inherited this tendency.

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patients were operated upon because of pelvic pathology, such as fibroids, endometriosis, or residues of pelvic infection. That the corpora lutea and endometriums can be normal under such circumstances has been shown by Sammartino and Gandolfo Herrera (1940), and Brewer and Jones (1941). Thus these specimens are considered to be normal. The entire corpus luteum was obtained in each instance. The associated endometrium was obtained in all but ten instances. Those specimens on which chemical analyses of the lipid content were made were quickly weighed and one-half of each was taken for cytologic study and half for chemical analysis. Fixation in all instances was begun within ten minutes after the tissues had been removed from their blood supply. Fixation in the various solutions was carried out in the refrigerator in order to retard the changes that occur in tissues after removal from their blood supply. The fixations used were aqueous-formol-chrome-sublimate, osmication after the preceding fixation, and neutral formalin.

Of the 97 corpora lutea studied 13 were in the proliferation stage, 31 in the vascularization stage, 36 in the so-called mature or blossom stage, and 17 in the so-called stage of regression after the onset of menstruation. In addition, 8 corpora lutea of early pregnancy were studied.

#### THE VASCULARITY OF THE CORPUS LUTEUM

The youngest specimen, approximately twenty-four hours old, has small capillaries extending into the granulosa cell layer. The growth of the capillaries is rapid as indicated by the numerous endothelial cells undergoing mitotic division. In specimens three days of age capillaries extend completely through the granulosa cell layer and project into the central cavity. The majority of the capillaries are distended with blood. Extravascular blood is marked throughout the entire cell layer, and in some regions small lakes are formed. The entire picture during these first three days of life of the corpus luteum is one of rapid and extensive vascularization of the granulosa lutein cell layer.

During the subsequent five or six days of life of the corpus luteum, which in the literature is termed the vascularization stage, the development of the vascular system reaches its peak. In corpora lutea five days of age, the tortuous capillaries are arranged in such a manner that they are immediately adjacent to most of the granulosa lutein cells. Each vessel is distended with blood (Fig. 1). In specimens of this age there is little extravascular blood in the granulosa lutein layer. There is an ingrowth of connective tissue along with the capillaries. This tissue, in conjunction with the vascular elements, projects into the central cavity, and during the next few days of life, the corpus luteum forms a lining separating the granulosa lutein cells from the central cavity. Until the corpus luteum is approximately seven to eight days of age the vessels throughout the granulosa lutein layer are filled with blood.

In specimens eight to ten days of age, there is a gradual diminution of the amount of blood within the vessels located in the granulosa lutein layer. The capillaries are more narrow and more straight (Fig. 2). Only a few capillaries in occasional isolated regions are dilated and filled with blood. There is little or no extravascular blood in the granulosa lutein cell layer. In the connective tissue core, however, the vessels are all dilated and filled with blood. There is also an increase in the amount of extravascular blood in this core.

In corpora lutea after the tenth day of life, there is little blood either within or without the vessels in the granulosa lutein layer (Fig.



3). Only an occasional capillary is found which contains any blood. They are for the most part collapsed. There is also a marked increase in the amount of connective tissue surrounding the vessels.

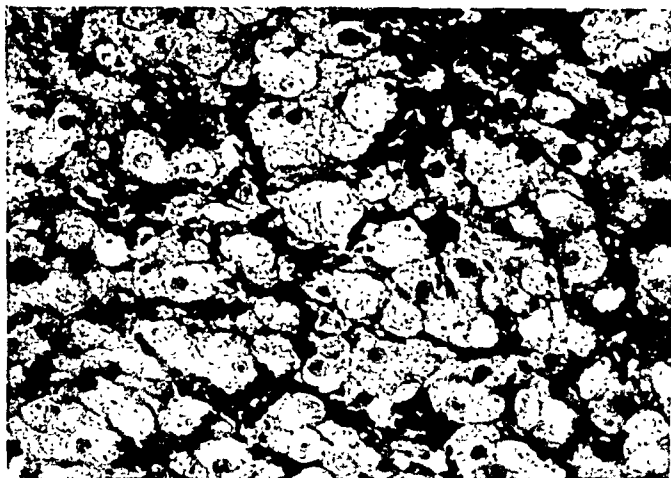


Fig. 1.—The vessels in the granulosa lutein layer are distended with blood (blood appears black in photomicrograph). The capillaries are arranged immediately adjacent to most of the granulosa lutein cells. There is some extravasation in this layer.  $\times 345.5$ . Patient 342, aged 46 years. Menstrual cycle twenty-eight to thirty days with four to five day flow. Specimen removed on eighteenth day of cycle. Estimated age of the corpus luteum is approximately five days.

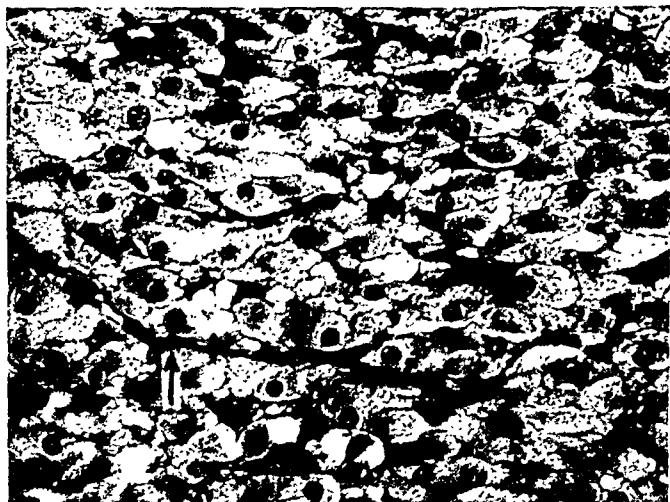


Fig. 2.—The vessels in the granulosa lutein layer are straight, narrow, and contain little blood (arrow). In many regions all the vessels are collapsed and empty.  $\times 345.5$ . Patient 337, aged 42 years. Menstrual cycles twenty-eight days in length. Flow lasts four to five days. Specimen removed on the twenty-first day of the cycle. Estimated age of the corpus luteum is approximately nine days.

The cessation of development of the vascular system throughout the granulosa lutein layer, the reduction in the blood in the vessels, the marked narrowness and straightness of the vessels, the collapsed capillaries, and the great increase in the amount of connective tissue surrounding the vessels are interpreted as evidence of regression of the vascular system. These changes begin to appear at about the eighth day of life of the corpus luteum.

In corpora lutea of early pregnancy, the above-described changes do not take place. There is instead a continuation of the development and functioning of the vascular system.

A review of the many descriptions of the vascularization stage of the human corpus luteum, as well as the findings reported here, indicate that a reduction in vascularity of the corpus luteum occurs at the end of the vascularization stage. During the so-called blossom stage all authors describe a marked reduction in the amount of blood in the granulosa lutein layer and regressive changes in the vascular system. According to this there is, during the previously so-called period of maximum function, a marked decrease in vascularity. This is not consistent with the known fact that for maximum function of any tissue, a maximum blood supply is required.

It is more sound to conclude, first, that the period of maximum function of the corpus luteum coincides with the period of greatest vascularity, which, in this instance, is the so-called vascularization stage;

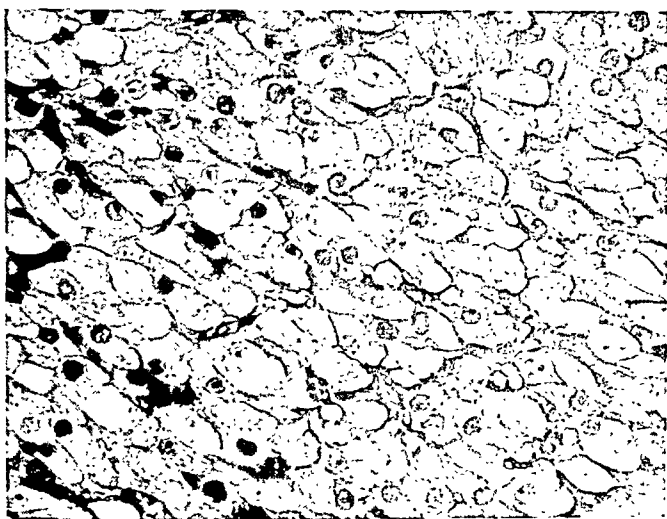


Fig. 3.—This corpus luteum, approximately eleven days of age, was removed on the twentieth day of the cycle. The capillaries are collapsed and empty.  $\times 345.5$ . The patient, No. 345, was 46 years of age. The menstrual cycles were twenty-eight days in length and the flow lasted three to five days.

and second, that when there is a decrease in the vascularity of the corpus luteum there is a simultaneous decrease in functional activity of that gland. It follows then, that the function of the human corpus luteum of menstruation begins to decrease at the termination of the vascularization stage. The reduced vascularity and the regressive changes of the vascular system during the period of life of the corpus luteum that has been called the blossom, or mature stage indicates, in reality, that this is the period of beginning regression of the gland.

#### THE GRANULOSA LUTEIN CELLS

The changes in the granulosa lutein cells that indicate functional activity appear simultaneously with the ingrowth of capillaries into that layer. With the steady increase in vascularity, the cells become larger and acquire mature functional characteristics. In corpora lutea approximately seven to eight days of age all of the granulosa lutein cells are not developed to the same degree as Meyer (1911 and 1932) has previously reported. In this stage, the cells contain many small lipid drop-

lets scattered through the cytoplasm. The greatest lipid content is observed in those cells along the border of the central cavity. The nuclei are large, vesicular, and round or oval.

Near the end of the vascularization stage (corpora lutea eight to nine days of age) some of the granulosa lutein cells begin to degenerate. In a typical specimen of this age group (No. 337) approximately nine days of age, there are rather frequent granulosa lutein cells that are large, have clear cytoplasm, and pyknotic nuclei (Fig. 4). The endometrium associated with this corpus luteum shows no evidence of regression. In specimens of this age group some lipid laden cells have nuclei that are pyknotic, while in others the nuclei are nearly normal. In later stages, the number of cells evidencing degeneration increases progressively. In Specimen 255, approximately eleven days of age, such

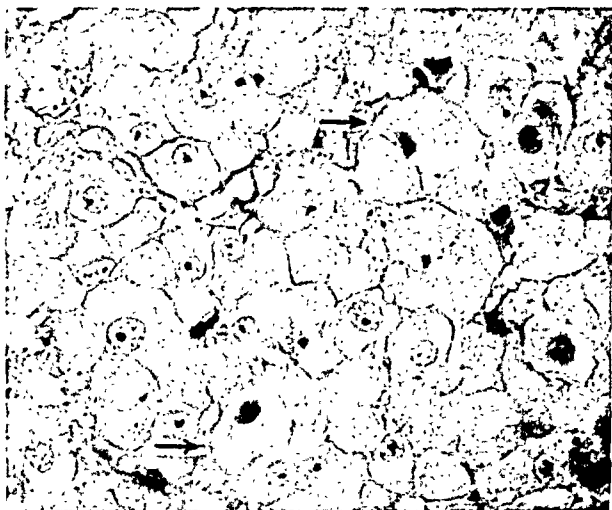


Fig. 4.—Near the end of the vascularization stage there are in the granulosa lutein layer large degenerating cells with clear cytoplasm and pyknotic nuclei. Two are shown here (arrows)  $\times 491$ . This corpus luteum, aged 9 days, was removed on the twenty-first day of the cycle. The patient, No. 337, aged 42 years, had cycles of twenty-eight days in length with four or five days' flow.

degenerating cells are more numerous and a greater number of nuclei are pyknotic (Fig. 5). These more extensive zones of degeneration are localized. The amount of lipid in most of the granulosa lutein cells is increased, and the droplets are larger. The endometrium of this specimen is shown in Fig. 6. Involution has begun as indicated by the squashed appearance of the glands and the absence of edema. Superficial infiltration of leucocytes and lymphocytes has not yet occurred.

During the eighth to the tenth day of life of the corpus luteum, many of the granulosa lutein cells continue to enlarge somewhat. Some of these cells are larger because of degenerative changes with an increase in the number and size of lipid droplets, while some are larger probably because of a continuation of their secretory function. From the eleventh or twelfth day on, however, the vast majority of all granulosa lutein cells shrink in size. In Specimen 149, which is typical of those approximately thirteen days of age, there are many large degenerating granulosa lutein cells. In addition, many cells are shrunk and have intact nuclei. Other shrunk cells have nuclei that are irregular in shape, stain poorly, and are variable in size (Fig. 7). The cytoplasm in these cells is vacuolated. The cell membranes are irregular. The visible lipid material

in increased. The endometrium is shown in Fig. 8. Involution has taken place, and there is some infiltration of leucocytes and lymphocytes superficially.

In corpora lutea removed just before the onset of menstruation (approximately fourteen days of age), the vast majority of the granulosa lutein cells are shrunk. Many retain intact nuclei. In Specimen 406,

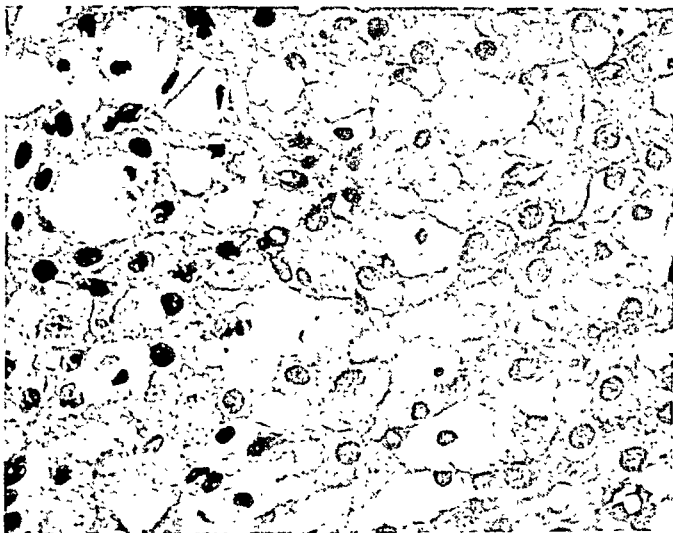


Fig. 5.—Degenerating granulosa lutein cells are numerous. There is no blood in the vessels of the granulosa lutein layer of this specimen.  $\times 491$ . The estimated age is approximately twelve days. The endometrium undergoing involution is shown in Fig. 6. This specimen was obtained from Patient 255, aged 35 years, on the twenty-seventh day of the cycle. The cycles were twenty-six to thirty-five days in length with five days' flow.



Fig. 6.—Involution in this endometrium has occurred as indicated by the squashed appearance of the glands and the loss of edema fluid. The regressing corpus luteum is shown in Fig. 5.

removed within six hours after the onset of menstruation, the cells are small; the nuclei are indistinct; the lipid content is increased; and the staining quality of the nuclei and cytoplasm is poor (Fig. 9). Most of the endometrium is still intact although the characteristic premenstrual loosening up of the tissue is apparent (Fig. 10). In the progressing

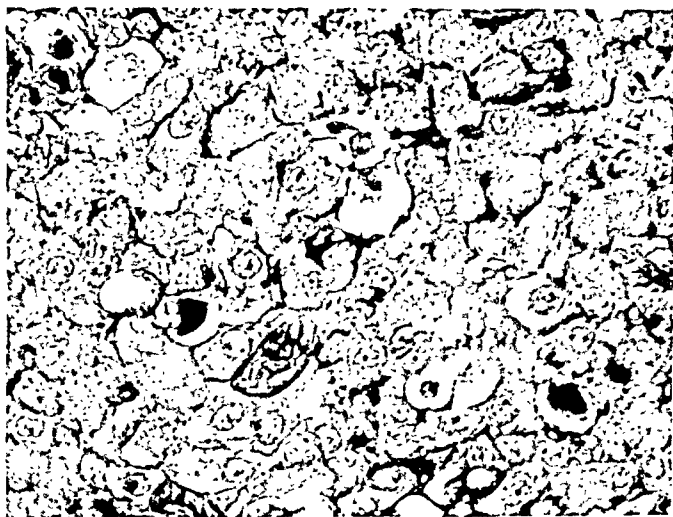


Fig. 7.—In this degenerating corpus luteum approximately thirteen days of age, the granulosa lutein cells are shrunken. Numerous cells have pyknotic nuclei and clear cytoplasm. The cell membranes are irregular and the connective tissue is increased.  $\times 491$ . The endometrium is shown in Fig. 8. The patient, No. 149, aged 36 years, was operated upon on the thirtieth day of her cycle. Her cycles were usually twenty-eight days in length with three or four days' flow.

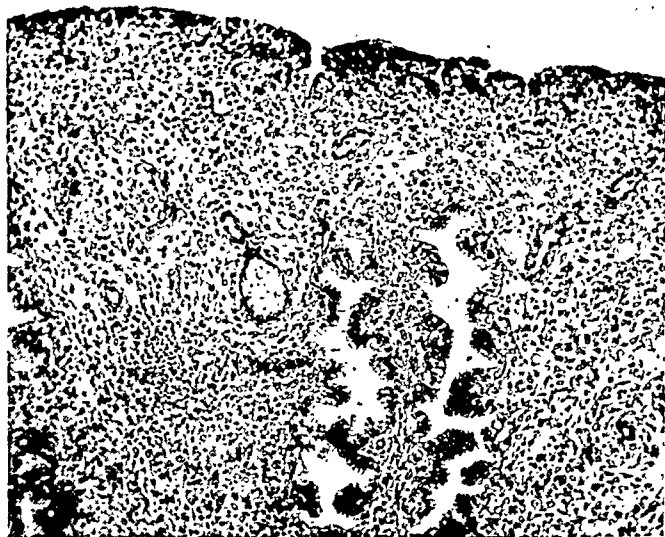


Fig. 8.—This photomicrograph shows the infiltration of leucocytes and lymphocytes that usually occurs two to three days before menstruation. The corpus luteum is shown in Fig. 7.

stages of death these changes in the corpus luteum are more profound. The cell membranes are finally lost and connective tissue replaces the granulosa lutein layer. Connective tissue invasion of the granulosa lutein layer is a continuous process from the time of ovulation. During regression of the gland, however, the invasion is more rapid.

The degenerative changes that characterize regression of the corpus luteum are fatty degeneration and simple atrophy of the granulosa lutein cells.

At about the eighth or ninth day a marked increase in visible lipids in the granulosa lutein cells is observed. During the subsequent existence

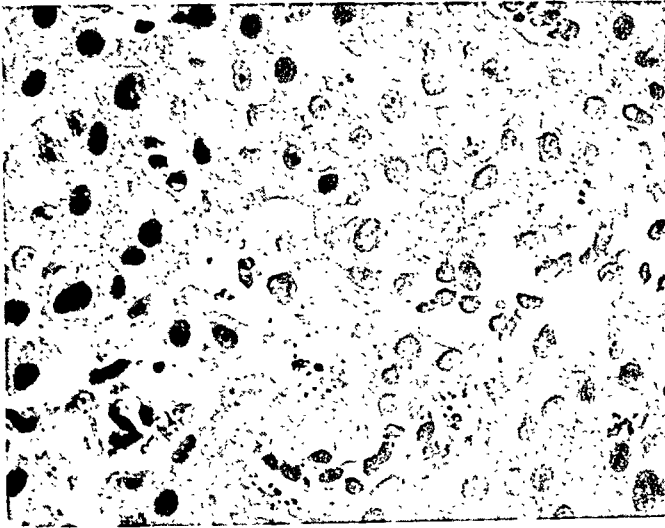


Fig. 9.—In this photomicrograph of the granulosa lutein layer of a specimen removed six hours after the onset of menstruation, the general staining qualities of the cells are markedly reduced, the cell membranes are indistinct, and the nuclei evidence pyknosis and karyorrhexis.  $\times 491$ . This patient, No. 406, aged 45 years, had cycles usually of thirty days with five or six days' flow. This cycle just completed was thirty-one days in length. A portion of the endometrium which has not yet desquamated is shown in Fig. 10.



Fig. 10.—This photomicrograph shows the loosening up of the stroma, the loss of edema, the collapsed glands, the infiltration of leucocytes and lymphocytes, and the extravasation which indicate impending menstrual slough. Desquamation has occurred in other portions. Menstruation began clinically six hours before operation. The corpus luteum is shown in Fig. 9.

of the corpus luteum, the lipid content increases. That the increase of lipid content is a part of a degenerative rather than a functional process is suggested by four things. First, the quantity of lipids increases steadily throughout the subsequent degeneration of the corpus luteum. Second, the lipids are most abundant in those cells showing histologic evidence of degeneration. Third, the lipid droplets are of various sizes and many are large globules in contrast to the fine droplets observed in earlier functional stages. Fourth, in the presence of continued or increased functional activity of the corpus luteum, such as occurs in pregnancy, no such increase in visible lipids occurs. In the granulosa lutein layer the simultaneous occurrence of fatty degeneration and reduced circulation suggests that the fatty changes are the result of anoxemia.

Simple atrophy is recognizable in the granulosa lutein cells of corpora lutea from eleven days of age on (Figs. 5, 7, and 9). This degenerative process, since it is a gradual one, may be assumed to have begun at least a day or two before the atrophic cells can be positively identified. This is necessarily true, since it is difficult to discern an actual reduction in the size of granulosa lutein cells because at the onset of degeneration the number of cells so involved is few. Furthermore, the marked irregularity and the characteristic jumbled arrangement of the lutein cells, and the plane of section in which the cells must unavoidably be cut adds to the difficulty of interpretation. It is only when a sufficient number of cells has undergone a sufficient degree of atrophy that this type of degeneration can be unequivocally demonstrated. As noted above, this can be done from the eleventh day of age of a corpus luteum on. Simple atrophy of the granulosa lutein cells is undoubtedly the result of anoxemia.

The progressive character of the degenerative changes in the granulosa lutein cells after the eighth day and the fact that if pregnancy intervenes such degenerative changes are at a minimum suggests that regression begins at the termination of the vascularization stage.

The observations on the associated endometriums demonstrate that regressive changes in the endometrium appear later in the cycle than do the regressive changes in the corpus luteum. This is due to the fact that there is a lag in the endometrial response both to corpus luteum stimulation and to the withdrawal of that stimulation. The regressive changes in the endometrium are observed here approximately four days before the onset of menstrual flow. Regression of the corpus luteum then must begin five or six days prior to menstruation, which time corresponds to the termination of the vascularization stage.

#### PHOSPHOLIPID AND CHOLESTEROL ESTER DETERMINATIONS

Chemical analyses were made by S. Weinhouse on 61 of the human corpora lutea in this presentation. Some of these specimens were not included in the previous report by Weinhouse and Brewer (1942). The chemical methods employed permitted the determination of exact values of the various lipids occurring in each individual specimen.

There is a gradual, steady increase in the phospholipid content from the time just after ovulation to about the tenth day of age of the corpus luteum (Fig. 11). The maximum value is 2 per cent of the fresh moist tissue. From the tenth day of life on there is a decline in the phospholipid content. On the basis of the established fact that the phospholipid content varies directly with the functional activity

of the tissue, it is concluded that the functional activity of the corpus luteum of menstruation reaches its maximum by the eighth or tenth day of its life. After this time, the decline of phospholipid values indicates a decrease in functional activity. In instances of pregnancy, the phospholipid values are increased in association with the increased functional activity of the corpus luteum.

During the first ten days of life of the corpus luteum, there is a slight decline in the cholesterol esters (Fig. 11). After the tenth day there is an abrupt increase. Near the onset of menstruation and after menstruation has started the increase of cholesterol esters is marked.

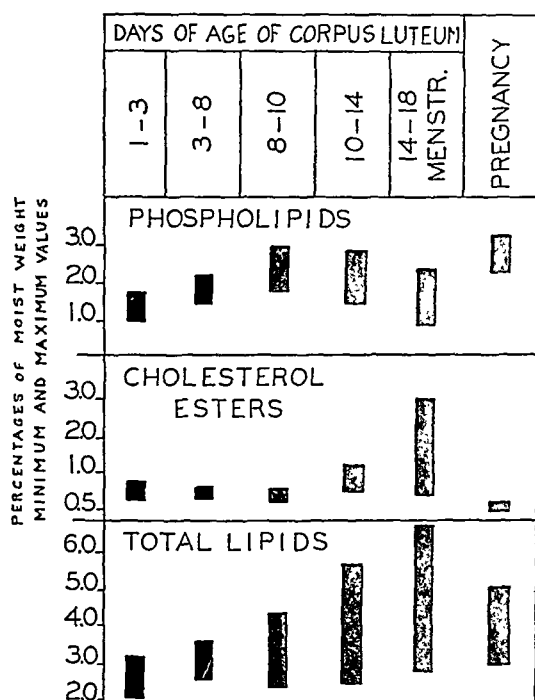


Fig. 11.—*a*, The phospholipid content increases until the tenth day after ovulation, after which it declines. In pregnancy the high phospholipid values indicate a greater degree of corpus luteum function. *b*, The cholesterol ester content remains low until the tenth day, after which it increases abruptly. In instances of pregnancy the minimal values obtained indicate continued functional activity. *c*, The total lipids increase constantly in corpora lutea of menstruation reaching the highest values in later stages of regression. The increase after the tenth day of life of the corpus luteum is the direct result of the increase in cholesterol ester content.

Since cholesterol esters increase in a degenerating tissue, it is concluded that the corpus luteum begins to regress about the ninth or tenth day of its life, and that it degenerates rapidly near the time of, during, and after menstruation. If pregnancy occurs and the gland does not degenerate, the values for cholesterol esters are minimal.

Thus, the chemical evidence suggests that the peak of corpus luteum function is reached during the vascularization stage and that degeneration begins at the termination of this stage.

#### SUMMARY AND CONCLUSIONS

During the first eight days of life of the corpus luteum of menstruation, there is a gradual increase in its functional activity. By the eighth to the tenth day all the evidence indicates that the peak of functional activity is reached. It is during this first eight to ten days



of life that the essential purpose of the corpus luteum of menstruation is carried out; namely, the preparation of the endometrium for implantation of the fertilized ovum. It is logical to postulate that the maximum function of the corpus luteum of menstruation would endure during this most essential period of its life. Greatest functional activity during this period is indicated by all the findings described in this report. This period of life of the corpus luteum has in the past been termed the vascularization stage. It might preferably be termed the period of essential function of the corpus luteum of menstruation.

If pregnancy occurs, the corpus luteum hormonal activity continues, and is undoubtedly greater than that which exists in a nonfertile cycle. This is indicated by several facts. In early pregnancy there is an increase in the vascularity of the corpus luteum. Fatty degeneration and degeneration by simple atrophy of the granulosa lutein cells are not features of corpora lutea of early pregnancy. Corpora lutea of early pregnancy have a high phospholipid content, and a minimal content of cholesterol esters. Greatest quantities of pregnanediol in the urine are obtained during pregnancy (Venning and Browne, 1937; Wilson, Randall, and Osterberg, 1939; Müller, 1940). The marked vascular and secretory development of the decidua vera also denote continued and greater corpus luteum stimulation.

If implantation does not occur by approximately the eighth day after ovulation, this particular ovulatory cycle will be a nonfertile one, since implantation, if it is to occur, takes place by this time (Rock, 1942). It is logical to assume that regression of the corpus luteum will begin at this time, since in the absence of fertilization and implantation, there is no further need for continued corpus luteum function.

It is true, as all the findings demonstrate, that some degree of functional activity of the corpus luteum is maintained after the eighth or tenth day of its life. This is due to the fact that all of the cells do not begin to degenerate simultaneously and that the rate at which degeneration progresses varies in the different cells. Those cells that are not involved, or are only partially involved in the degenerating processes, continue to function. Since they are mature cells, they undoubtedly function efficiently. As a consequence, fewer cells are required to maintain the corpus luteum functional activity at a high level. The functional activity of the gland is reduced only when a sufficient number of cells has undergone a sufficient degree of degeneration. Definite reduction of functional activity can be recognized by the tenth or eleventh day of age of the corpus luteum. It is apparent by deductive reasoning as well as by interpretation of the facts described here that actual degeneration must begin, therefore, before the tenth or eleventh day of life of the corpus luteum. The studies on the urinary excretion of sodium pregnanediol glucuronidate by Venning and Browne (1937), Wilson, Randall, and Osterberg (1939), and Müller (1940) substantiate this. Definite regressive changes appear at approximately the

# THE USE OF ESTROGENS IN THE TREATMENT OF LEUCOPLAKIA, KRAUROSIS, AND SENILE VAGINITIS

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**P**RURITUS VULVAE, being a symptom and not a disease, has many etiologic factors: some systemic, such as diabetes; some hygienic, such as uncleanness; and some local, such as leucoplakia and kraurosis vulvae.

It is with the local factors only that we are concerned in this discussion for, obviously, these are the only ones which might be susceptible to estrogen therapy.

Investigation of the literature discloses that there is considerable confusion concerning local diseases of the vulva and vagina, generally due, apparently, to a lack of understanding of the identities of two of the most frequent diseases of this area, leucoplakia and kraurosis.

Ever since the latter part of the last century, when Breisky<sup>1</sup> (1885) first described a disease which he termed "kraurosis vulvae," there has been vagueness as to the identity of this condition. In 1909, Bonney devoted three Hunterian lectures to a discussion of kraurosis vulvae and leucoplakic vulvitis, the disease with which it had, and has, been frequently confused, and in the same year leucoplakic vulvitis was clearly identified and described in a classic paper by Berkeley and Bonney.<sup>2</sup> To quote their original description: "Leukoplakic vulvitis is to be defined as a chronic inflammatory condition of unknown origin characterized in its early stages by marked hyperemia and cellular activity, and in its later phases by marked epithelial hypertrophy and a thickened, sclerosed and retracted condition of the subepithelial tissue. Its distribution varies with its severity and time of incidence. In a well-marked case the whole of the vulva may be implicated with the exception of the vestibule and orifice of the urethra *which are never affected*, and not only may the labia majora, minora, anterior and posterior commissures and the clitoris suffer, but the disease may even spread laterally to the folds of the thighs and posteriorly over the perineum and skin surrounding the anus."

In contrast to this, we have their description of kraurosis: "Kraurosis vulvae consists of an atrophic condition of the vulva, associated clinically with stenosis of the vaginal orifice, and pathologically with certain changes in the dermis. The labia minora, vestibule, orifice of the urethra, and that of the vagina are always affected, the hood of the clitoris sometimes. The skin on the outer surface of the labia

of the lutein cells, because this hinders to a certain degree the secretion as well as the bleeding into the cavity. One finds fine lipid granules in the granulosa cells, but these disappear more and more as the cells get larger and the nuclei appear vesicular. Since the same process goes on in pregnancy, my conclusion seems justified that these signs mean high degree of function. The findings of Chydenius of the finer cell structure (1926) supported my conception.

My first conception (1913), that the maturity or "bloom" extended from the seventeenth day until one or two days before menstruation, I modified later on, because I found the lutein cells in the inner layers already in regression by the twenty-second to twenty-six days. The term function I used always in connection with the behavior of the endometrium, but as menstruation I considered not only the bleeding but also the preparatory stage.

I agree with Dr. Brewer that we should answer the question of the nature of function principally from the point of view of fertility in general and of the nidation especially. I quote what I said in 1913, that "the culmination of the premenstrual development of the endometrium is not the stage of preparation for the nidation of the ovum. Preparation for nidation rather should occur at about the middle point between two menstruations, i.e., at the beginning of the premenstrual swelling of the mucosa. The culmination of the premenstrual phase would therefore be only the introduction to menstruation.

We first found the histologic evidence of regression of the corpus luteum on the twenty-second to twenty-fourth days of the normal cycle, as shown by vacuolization of the cytoplasm by large fat droplets in the inner rows of the lutein layer. Later evidences of regression during menstruation (softening of the fibrils, obstruction of the vessels, shrinking and sclerosis of the fibrils) appear first centrally and progress to the periphery.

The third of Dr. Brewer's points, namely the chemical analysis of the corpus luteum, is of special interest because for many years we endeavored to clear up the quantitative differences between the histochemically demonstrable lipoids and the real chemical content. We consulted authorities for the best methods and co-operated with highly trained chemists. The total content of cholesterol during the cycle is at first low, then it increases until "bloom" and until menstruation. The increase is due to the free cholesterol and not the cholesterol ester. During pregnancy the total cholesterol content is less, and it decreases more and more toward the end of pregnancy. The fatty acid changes considerably from case to case, but not in the various stages or in high degrees of regression. Lecithin increases until the histologic "bloom" occurs and decreases strikingly after menstruation, but in pregnancy the lecithin content is high and becomes very high near the end of pregnancy. The total amount of the lipoids does not differ essentially in the various stages of the cycle. More striking is the microchemically visible amount which is known to be high only during the time of regression. It is recognizable as big droplets at first found locally in single cells of the innermost layers. This progresses to the peripheral layers and after the menstruation involves the whole corpus luteum.

Stained lipoids are stored as very small particles before they accumulate in the cytoplasm. The invisible lipids are used for hormonal function. Large droplets mean regression.

To prove an early regression of the corpus luteum as a physiologic process, one must exclude damage, especially such as pressure by a myoma, and one must examine the basal part of the corpus luteum, because the superficial part is very often damaged. This may occur at any time of the cycle in large areas in the superficially prominent or capsular parts and it may be compared to the regression in the capsular part of an implanted ovum. Cystic corpora lutea and those with hemorrhage are also often damaged and therefore useless for study of normal physiology. The beginning of the regression does not mean cessation of the func-

eighth to the tenth day. This time coincides with the termination of the so-called vascularization stage, or as suggested here, the termination of the period of essential function of the corpus luteum. These regressive changes are:

1. A marked decrease in the amount of blood in the vessels of the granulosa lutein layer and regressive changes in the vascular system.
2. Fatty degeneration and degeneration by simple atrophy of the granulosa lutein cells.
3. Increase in the amount of visible lipids in the granulosa lutein cells.
4. A sharp increase in cholesterol esters and a gradual diminution of the phospholipid content, as determined chemically.
5. Regressive changes in the endometrium.
6. A decrease in the amount of pregnanediol excreted in the urine, as determined by other workers.

Thus, since the peak of function is past, since the essential function is terminated, and since definite degeneration has set in, it is concluded that regression of the corpus luteum of menstruation sets in at the termination of the vascularization stage at approximately the eighth day of its life.

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104 SOUTH MICHIGAN AVENUE

#### DISCUSSION

DR. ROBERT MEYER, MINNEAPOLIS, MINN.—Dr. Brewer took exception to the idea of the stage of maturity or "bloom." These terms I used for the stage in which the connective tissue *begins* to cover the innermost layer of lutein cells. In the same way I applied the term "stage of proliferation" to the *beginning* of the striking multilayering of the granulosa cells after the rupture of the follicle, although the proliferation is already evident before rupture, and also, though to a lesser degree, later during the vascularization. Since the proliferation stage is short, one finds it only in follicles and not in the yellow body.

The term "maturity stage" I introduced in connection with two histological processes. In the beginning of the stage, which I called the stage of vascularization, the capillaries invade the proliferated granulosa, for the high point of internal secretion can only be obtained after the production of an arteriovenous network. The delivery of hormone into the blood is aided by the covering of the inner layer

fourteenth day. It is interesting that our time relationships, based on hormone changes as evidenced by urinary studies, should tally so closely with Dr. Brewer's, based on an entirely different type of investigation.

DR. JOHN ROCK, BROOKLINE, MASS.—In studying the corpora lutea from the seven normal previllous and villous human ova of 7.5 to 16.5 days of age, Miss Adams, our technician, and Dr. Hertig detected a decreased amount of neutral fat in the granulosa lutein cells when compared to the amount in the control non-pregnant corpora lutea of the twentieth to twenty-second day (sixth to eighth day according to Brewer's terminology) of the menstrual cycle.

In the nonpregnant, twentieth to twenty-second-day stages, they found a beginning nonfatty peripheral vacuolization of the granulosa lutein cells. With the onset of pregnancy this supposed evidence of active secretion was seen to increase and to remain a prominent feature throughout at least the first six weeks in the life of the corpus luteum.

Dr. Hertig has suggested therefore that the twenty-second day of the twenty-seven-day menstrual cycle (i.e., with catamenia on the twenty-eighth day), or the eighth day in the luteal phase of any cycle, is the critical point in the life of the corpus luteum. He believes that at this time implantation of the fertilized ovum, in some way not at present fully understood, but probably by its direct influence on the corpus luteum, causes the latter to continue and indeed to increase its secretory function, thereby postponing the degenerative and other changes which Dr. Brewer has covered in his paper.

DR. BREWER (closing).—It is an honor for one who is more or less beginning his work to have the privilege of having the primary author discuss his paper. It is to Dr. Meyer that we are all indebted for the essential work on the corpus luteum.

tion of the whole corpus luteum, the outer layers of which may be well preserved for a much longer time.

The histologic appearance of the endometrium is occasionally not an absolutely reliable indicator of the functional potency of the corpus luteum and vice versa. In some cases described by Bartelmez and also in some demonstrated by myself, the corpus luteum histologically showed no regression some days after menstruation which occurred at the expected time. On the contrary, in other cases Bartelmez found the regression of corpus luteum without menstruation. This means that some unknown factors are interposed between the two organs, corpus luteum and endometrium, such as nerve controls or the internal secretion of other organs.

I believe it is of the greatest importance to stress the fact that the goal of all these processes is naturally pregnancy, and that menstruation is the sign of failure. Great difficulty is presented by the constitutional variations in individuals, which cause obvious differences of interpretation. Perhaps no other physiologic conditions are less balanced and stabilized. They are relatively recent acquisitions in phylogeny. The hormonal accord of the sexual procedures fluctuates between the physiologic and the pathologic.

DR. GEORGE VAN S. SMITH, BROOKLINE, MASS.—Mrs. Smith and I have found that luteal activity is reflected by characteristic changes in the amounts and partition of the urinary estrogens. These changes, corroborating Dr. Brewer's conclusions, point to maximum secretion of progesterin between the fifteen and twenty-first days of a twenty-eight-day cycle with a peak between the nineteenth and twenty-first days.

What makes the corpus luteum wax and wane? From our studies of the relation between progesterone and estrogen metabolism we have formulated a plausible explanation. Progesterone reduces the rate of estrogen destruction in the body. Experimentally, estrogens may be so administered as to enhance and prolong luteal activity through stimulating the secretion of a pituitary luteinizer. Both in the menstrual cycle and in pregnancy the available evidence indicates that increases of estrogen secretion precede and accompany increases of progesterin. We have come upon a factor in the urine of women which has a pituitary-stimulating effect similar to the estrogens and have concluded that it is formed as a result of estrogen breakdown and that it, rather than estrogens per se, is responsible for the observed luteal response to administered estrogens. It is not a pituitary substance, being heat stabile and ineffective in hypophysectomized rats. It is non-estrogenic but is found in the urine at the times when our studies indicate rapid destruction of estrogen, for example, during menstruation and the follicular phase of normal cycles and after the injection of estrogen in surgical castrates. In summary, we are well along on a trail of evidence to show that whenever estrogen is being rapidly destroyed a substance is formed which stimulates pituitary luteinizing activity and thus corpus luteum function and that, by reducing the rate of estrogen degradation, the corpus luteum prevents the production of this substance which is necessary for its survival.

We would explain the ovarian cycle, therefore, as follows: At the start of menstruation there is a sudden marked increase in the rate of estrogen degradation accountable to estrogen production in the absence of progesterin. This sudden metabolic shift, which continues into the follicular phase, supplies the above-described factor as a result of which the pituitary secretes the luteinizing hormone, so necessary for ovulation and corpus luteum growth. Our studies indicate that by the twenty-first day of a twenty-eight-day cycle a minimal amount of estrogen is being destroyed due to maximum progesterin secretion. The result is withdrawal of pituitary stimulation by the estrogen breakdown factor and consequent regression of the corpus luteum. The twenty-first day of a twenty-eight-day cycle would be the seventh to eighth day of life of the corpus luteum if ovulation occurs on the

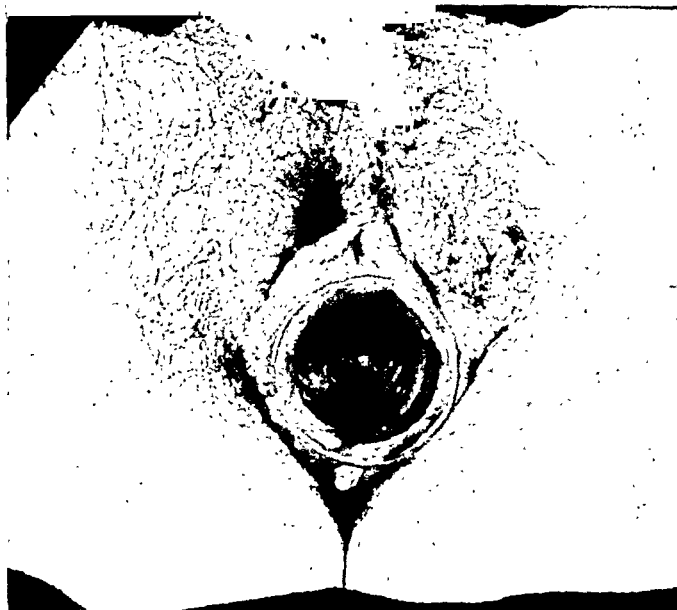


Fig. 1.—Typical end-result after the Frank-Geist "satchel handle" operation for congenital absence of the vagina. (Note slight scarring of area from which the skin flap was taken.)

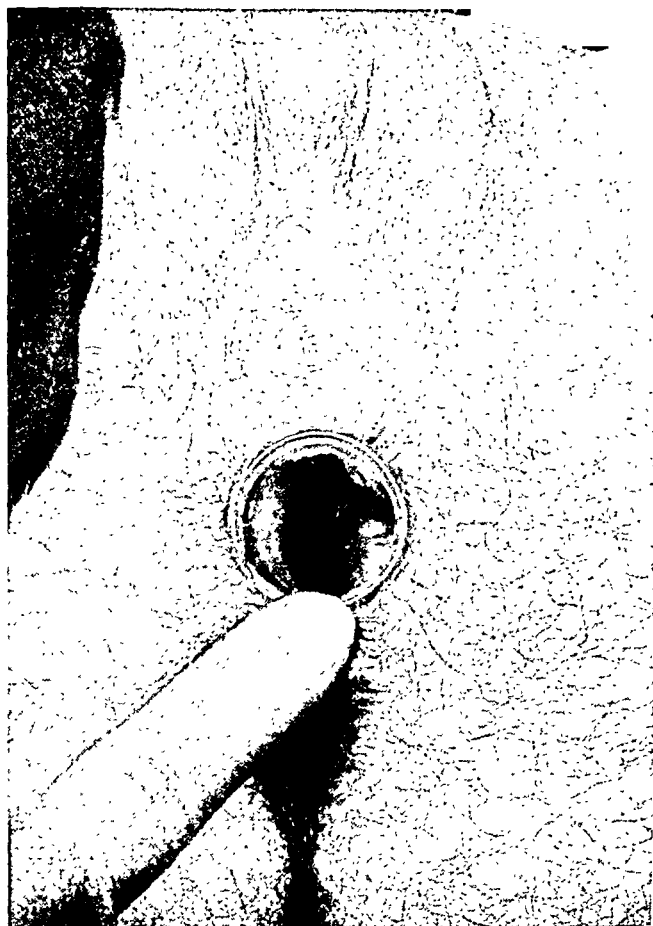


Fig. 2.—End-result in a pseudohermaphrodite. Frank-Geist operation obviously impossible, because of profuse hair distribution. (Note developmental defect of normal labia.)

## PARTIAL CONGENITAL APLASIA OF THE VAGINA\*

WALTER T. DANNREUTHER, M.D., F.A.C.S., NEW YORK, N. Y.

*(From the Department of Gynecology, New York Post-Graduate Medical School and Hospital, Columbia University)*

WITHIN the past twelve years, I have seen 12 cases of congenital absence of the vagina. Four of these were complete, 5 could be legitimately classified as a partial aplasia, and 3 were really developmental defects in pseudohermaphrodites. Three of the first 4 patients were subjected to the Frank-Geist "satchel-handle" operation with highly satisfactory results, all 3 being married; twelve years, five years, and one year, respectively. A colpoplasty operation was not suggested to the other patient since she was thirty-four years old, devoid of secondary female characteristics, and had no sex urge. Four of the 5 young women with a partial aplasia were operated upon and these constitute the subject of this presentation. The other was 27 years old, had been married three years, and had submitted to an inadequate plastic procedure elsewhere one year and a half previously with a poor result, but refused further surgical intervention. One of the three pseudohermaphrodites was operated upon against my better judgment because of her insistence, and this case is described briefly because it is the only instance in which I have transplanted the fetal membranes to line a newly created vaginal canal. The end result was surprisingly gratifying.

The patient was 22 years old and had never menstruated. At the age of four a general surgeon had opened the abdomen for the sole purpose of determining her sex. He reported to the parents that a vestigial uterus and two small ovaries were found high in the pelvis. At the age of twelve, after a two weeks' study at another hospital she was again pronounced a female. When this girl came under my observation in January, 1939, she insisted that an attempt be made to provide her with a vaginal canal because of her sex urge. Her urine contained 21.4 R. U. of estrin in a twenty-four-hour specimen and 16.1 R. U. per liter. Although there was scant anatomic evidence of female external genitalia and relatively little available space on the perineum between the lower margin of the urinary meatus and anus, the enlarged clitoris was almost completely amputated, and the space between the urethra, bladder, and rectum cautiously approached through a transverse perineal incision just above a miniature fourchette. The contemplated dissection seemed so hazardous that roentgenograms were taken with a catheter in the urethra and air distention of the rectum before the operation. This visualization of the field was of material aid in avoiding injury to the urethra, bladder, and rectum. After insinuating the exploring fingers between these structures up to the peritoneum, the

\*Read at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.



mally small introitus and an extremely rigid and sensitive hymen, which in some cases is situated from 1 to 3 cm. above its normal location. All four patients were treated in the same way, by making a transverse incision through the obstructing upper limit of mucous membrane, progressive finger dissection between the bladder and rectum up to the peritoneum, and inserting the largest size glass phallus which the newly created space would accommodate. The glass vaginal obturators I have used are shaped much like the anatomic phallus, except that they have a little indentation near the outer margin which precludes pressure on the overlying urethra (Fig. 3).

The first patient, single, aged 28 years, was operated upon in August, 1939, and has been happily married since March, 1940. She reports that coitus is normal in every way, but is still wearing her glass plug. The second patient was single, aged 18 years, was operated upon in February, 1940, and has worn the plug continuously ever since. The third patient, aged 23 years, was operated upon in March, 1941,

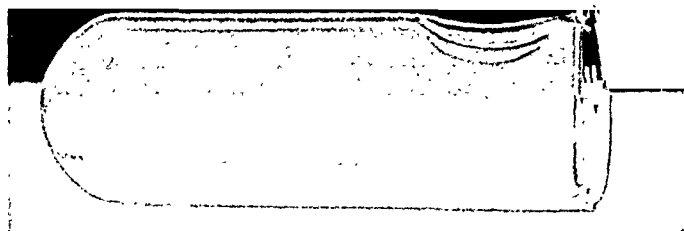


Fig. 3.—Glass tube used for maintaining vaginal dilatation. (Note indentation near outer margin to avoid pressure on overlying urethra.)

immediately after her husband had left her, because after four years of marriage, attempts at coitus had never been successful. Although hopeful that correction of the anatomic defect would enable her to re-establish her home, the husband failed to return. However, she was subsequently treated by another physician for an acute gonococcal vaginitis. She is a timid individual, who does not tolerate discomfort well and consequently failed to maintain enough pressure on the vaginal obturator, so that in October, 1941, it was necessary to again enlarge the upper end of the canal, which showed evidence of moderate contraction. In April, 1942, she developed an inguinal hernia and was operated upon in another city. The surgeon reports: "I found a tube and ovary which appeared normal, in the inguinal canal, separated the tube and ovary from the surrounding tissues of the canal, and replaced them in the abdominal cavity. On palpation through the internal ring with one finger, I thought I felt the fundus of a small uterus, but could not be sure. I did a regular Ferguson repair of the hernia." The fourth patient, aged 20 years, had been separated from her husband after four months of marriage and was operated upon in October, 1941. After wearing a large plug for three months, the husband returned and coitus has been normal ever since.

space thus developed was lined by implanting a generous section of fetal membrane, taken from another patient delivered by elective cesarean section within the previous hour, as suggested by Burger. (Membranes after rupture would obviously be useless because they would not be sterile.) The membrane was held in position with a glass phallus of appropriate size. Inspection at the end of two weeks disclosed small islands of epithelium throughout the canal as though pinch grafts had been transplanted. Although the cosmetic result is more picturesque than perfect, the artificial vagina appears functionally satisfactory (Fig. 2).

Many methods of establishing an artificial vaginal canal have been devised during the past century. They all include a transverse incision of the occluding membrane and separation of the cellular connective tissue between the bladder and rectum. Additional steps suggested, and their leading exponents are as follows:

Distending the canal with gauze packing, balsa wood, or Pyrex glass (Dupuytren, Kanter, Wharton, Meigs)

Implantation of isografts (Mackenrodt)

Transplantation of rectum (Snequireff, Popow, Menge, Schubert)

Transplantation of ileum (Baldwin)

Transplantation of flaps from the labia (Bumm, Puppel, Graves)

Transplantation of skin flaps from the thigh (Beck, Frank-Geist, Grad)

Implantation of fetal membranes (Burger)

Transplantation of Thiersch skin grafts (Kirschner-Wagner) and with mastic solution (Counsellor)

One of the originators of the Frank-Geist operation has reported five recent cases in which he secured a satisfactory canal, without an incision or operation, by forcing the mucous membrane of the obstructing partition inward by means of glass test tubes. The patient is taught to introduce a narrow tube into the hymenal ring with backward and inward pressure. After one week the direction of the pressure is changed to that of the normal vaginal axis, and as dilatation with indentation progresses, larger tubes are used until the new canal is adequate for coitus. This bloodless and simple method would seem the most desirable of all, but unfortunately proved entirely inadequate in the only two cases in which I have tried it, probably because of the unwillingness of the patients to subject themselves to so much controllable discomfort.

The four patients operated upon for partial aplasia of the vagina had certain features in common. They were all young, attractive girls, with a typical female body contour, well-developed breasts, and pronounced secondary sex characteristics. None had ever menstruated. The external genitals were well developed, and each had a rudimentary vagina about one inch in depth. The blind end of this tiny pouch was apparently a composite of occluding membrane and tough hymenal partition. True partial congenital aplasia should not be confused with a somewhat similar condition seen far more often, in which there is simply a developmental gynatresia of a vaginal canal of normal length with an abnor-

elaborate and hazardous operations involving an intestinal resection can be completely discarded as unnecessary.

580 PARK AVENUE

### DISCUSSION.

DR. JOHN E. HOBBS, St. Louis, Mo. (By Invitation).—The operative procedures to create an artificial vagina are limited as far as I am concerned to two and possibly a third method. In all cases where there is an absence of the uterus or a hypoplastic uterus that does not function, I believe Frank's method of forcing the mucous membrane of the obstructing wall inward by means of a glass test tube should be attempted. The method is simple, not dangerous and nonconfining. If results are not satisfactory, one has not created any additional difficulty for any operative method desired. If Frank's method fails in these cases, or if a functioning uterus is present, it seems to me that the choice of operative procedure is the one selected by Dr. Dannreuther in the cases just described, that is a variation of the method championed by Wharton and Meigs. I wish to report briefly the two cases.

CASE 1.—M. P., aged 18 years, sought medical attention because she had not menstruated, and her local doctor told her she had an imperforate hymen. The physical examination revealed a normal girl with the exception of the lack of a vagina and uterus. She had hypertrophy of the clitoris and labia minora. There was a small dimple above the fourchette without a vaginal opening. A rectal examination revealed no evidence of hematocolpos. A small firm nodule 2 x 2.5 cm. was felt in the uterine region. A cordlike structure was palpated in both adnexal regions with what was considered to be normal gonads at either end. She was engaged to be married and wanted surgical intervention.

A transverse incision was made in the obstructing membrane and a tunnel was constructed between the bladder and rectum up to the nodule felt in the uterine area. A canal 4 inches deep and 2 fingers in breadth was formed. An obturator of dental wax was made and full thickness grafts from the inner aspects of the labia minora were cemented (epithelial surface only) to the obturator with rubber cement. The obturator with the grafts on it was inserted into the canal and maintained in position by placing an eye-screw in the outer end of the dental wax dilator. A small rubber tube was passed through the eye-screw, carried between the buttocks and thighs and each end of the tubing was attached to a band placed around the body above the ilia. The patient could wear the obturator with comfort, void with ease and without disturbing the dilator. She could have pitcher douches without ever any chance of the obturator being displaced. The dilator was removed on the 18th day and islands of epithelium appeared in the tract. Rapidly the tract became epithelized.

In about three months after the operation she married, and her sexual life has been normal for about three years. I received a letter from her a few days ago, stating she is happily married and enjoys coitus.

CASE 2.—M. G., aged 16 years. At 12 years of age this patient started having severe cramps and fainting every month but never any flow. In May, 1941, her local doctor incised what he thought was an imperforate hymen and found there was a total lack of a vagina. He made a small tunnel between the bladder and rectum, and after reaching what he thought was a cervix, a considerable amount of old blood came out. He placed a gauze pack in the canal but it gradually became constricted. She had two periods of scant flow after this procedure. At the time I saw her, two and one-half months later, she appeared to be a normal girl, well developed and in good health. On examination of the genitals the labia minora were hypertrophied, and the clitoris normal. The canal was completely

The outcome can be regarded as quite satisfactory in all four cases since the canals were well epithelized within three months; three of the patients are using their new canals physiologically, and the other one has adequate space for normal coitus. It is universally recognized that all artificial canals manifest a tendency to contraction if dilatation is not maintained for a long time. Hence, it is advisable to keep the patients under observation and to insist that they wear the glass phallus for many months if married and continuously if single. Faithful co-operation is important, for if the patient shrinks from a mild discomfort and fails to exert sufficient pressure on the vaginal obturator, contraction may occur. In the cases cited there can be no doubt that the squamous cell epithelium lining the upper part of the vaginal recess crept in from the margins of the lower vaginal area which had been incised and stretched. Burger contends that when a new canal is lined with fetal membranes, there is actual epithelial transformation, because epithelization takes place as early as six days after the membranes have been implanted, and this is too soon for extensive proliferation to occur. He believes that the amniotic epithelium possesses the same physiologic characteristics as the epidermis, both showing the presence of glycogen. Sections of fetal membranes were used as transplants by Burger's ophthalmologic colleagues at his suggestion in four cases of symblepharon, to replace the lost conjunctiva, with subsequent development of stratified epithelium.

In the earliest cases of congenital absence of the vagina reported in the literature, the operation consisted of simple dissection of the adventitious connective tissue between the bladder and rectum, followed by packing the newly created space with gauze. This procedure was described by Dupuytren as early as 1817, but he and others soon found that this method was followed by prompt contraction and epithelization. Wharton has reported excellent results in 65 per cent of cases after the introduction of a balsa wood obturator covered with two layers of condom rubber, and Meigs has used Pyrex glass plugs in the same way. Packing the canal with any soft and compressible material predisposes to failure because there is no resistance to rapid contraction which occurs before epithelization can progress to any great extent. Since the squamous cells must proliferate from the margins of the introitus, it seems logical to continue the use of some variety of skin transplant in cases of complete absence of the vagina, or to adopt Frank's suggestion to apply pressure with test tubes on the occluding membrane without incision, if the patient can be induced to apply and maintain sufficient pressure. In cases of partial aplasia, however, a serviceable canal can be prepared within two or three months by introducing a glass plug into the newly created space between the bladder and rectum, with little discomfort to the patient. Regardless of each individual operator's preference for a particular technique, it seems quite evident that the

majora between the labia majora and folds of the thigh covering the perineum and surrounding the anus *is never affected.*"

The distribution of these lesions then is quite different, leucoplakia affecting the skin around the vulva and kraurosis affecting the mucous membrane within the boundaries of the labia minora.

The pathology of the two diseases is also quite different, leucoplakia being characterized by a swelling and hyperemia of the epithelium and later by a pronounced cellular proliferation of the subepithelial tissue. Still later the subepithelial tissue becomes fibrotic and the basal layers of the epithelium markedly hypertrophied. The continued sclerosis of the subepithelial tissue produces the characteristic smooth and shiny white appearance which may become cracked, fissured, and ulcerated.

Kraurosis, on the other hand, produces an extremely thin epithelium with atrophic papillae which in many places have almost disappeared. A retention of normal elastic tissue and a massive infiltration of white cells of all types are also identifying characteristics. This disease is much more closely akin to simple senile vaginitis and may be an aftermath of the latter and have the same etiology, i.e., estrogen depletion. A long time before the physiology of estrogens was well known, kraurosis was thought to be due to ovarian failure, and from a physiologic point of view, it would be reasonable to suppose that estrogen therapy would have a more beneficial effect on the symptoms of this disease than on those of leucoplakic vulvitis.

Since there is evidence that estrogen used as an inunction has a local effect on the tissues, it has been thought that its local application to the affected areas might be more beneficial than parenteral or oral administration.

Various estrogens have been used in inunctions for this purpose in both leucoplakia and kraurosis. As a rule, no attempts have been made recently to distinguish between these diseases, and both have been called variations of chronic atrophic dermatitis (Adair and Davis<sup>3</sup>).

Kerkovian<sup>4</sup> treated 4 patients with a salve containing 0.5 mg. of estradiol per c.c. of sesame oil base, applying 1 c.c. of the salve at two- to six-day intervals with beneficial results. A larger series of 21 patients treated with dihydroxyestrin salve was reported by Finkler and Antopol<sup>5</sup> who followed their patients with vaginal biopsies and smears. All but 6 were relieved by treatment and 1 patient, who received approximately 100,000 R.U. of estrogen by inunction in three months, developed a recurrence of uterine bleeding following the menopause.

Mishell and Motyloff, using estriol or trihydroxyestrin, noticed improvement in all of 3 patients treated. The dosage was not indicated.

Within the past two years, 21 patients complaining of pruritus vulvae have been admitted to an endocrine clinic of the Sloane Hospital for Women.

closed, and only a dimple existed above a well-formed fourchette. A transverse incision was made, and again the rectum and vagina were separated by both blunt and sharp dissection. There was considerable scar tissue which had to be freed by sharp dissection. At a distance of  $3\frac{1}{2}$  inches a tight constriction was reached which was dilated with great difficulty. I could not convince myself that this was a cervix. A uterine sound was passed beyond the constriction to a depth of  $2\frac{1}{2}$  inches, which I believed was the upper limit of the vagina. I could never get the constriction dilated enough to expose a cervix above. Two full thickness grafts, about  $2 \times 3$  cm., were removed from the inner aspects of the labia minora and tied with fine catgut about a large test tube,  $1\frac{1}{2}$  inches in diameter. The tube was held in position by placing a rubber stopper in the tube and an eye screw in the rubber stopper. A small rubber tube was placed through the eye screw and secured as described in the other case. The test tube was removed the first time in one week. At that time the canal was 5 inches long and admitted 2 fingers. I could not be certain whether or not the grafts were growing. There was great difficulty in keeping the upper portion of the canal dilated. Finally a biopsy was taken and the constricted portion contained cervical glands. Normal endometrium was obtained from higher up. Therefore, the constricted portion was cervix, which was and still is flush with the vaginal walls. The vagina then measured about  $3\frac{1}{2}$  inches. The canal is completely epithelized and has now been lengthened to about  $4\frac{1}{2}$  inches by pressure of the tube worn at night. The patient menstruates regularly and without pain.

My observation of these two cases convinces me that any type of graft is unnecessary. The vestibular epithelium will grow in and line the tract satisfactorily.

The third method of implantation of fetal membranes, as proposed by Burger and used in one case by Dr. Dannreuther, is most intriguing. However, I have always been skeptical about the growth and persistence of this tissue. Brown and McDowell have shown that homotransplants of skin that appear to grow early always disintegrate in three to six weeks, and then the epithelium grows in from the edges at a rapid rate, giving the ordinary observer the idea that the graft has persisted. It is Brown's opinion that no homotransplants persists, even homotransplants of cartilage become fibrotic months afterward. If the entire tract can become lined in four to six weeks without any epithelial transplants, it seems difficult for one to evaluate with any certainty the value of transplants. However, if it were established that fetal membranes do not grow or persist it seems to me the membrane might serve as a dressing to the raw surfaces and perhaps serve as a guide for the ingrowing epithelium. In collaboration with Brown and McDowell, I have some investigative work in progress in an attempt to determine the growth and viability of fetal membranes when transplanted.

DR. NATHAN P. SEARS, SYRACUSE, N. Y.—I have seen 8 cases which might well be discussed at this time. Six of the patients had complete absence of the vagina; one had a partial aplasia, and the other appeared to be a true hermaphrodite. The six cases of complete aplasia were treated in the following manner:

CASE 1.—A well developed, normal girl of 19 years with female characteristics had never menstruated. Without a pelvic examination she was given considerable ovarian hormone by a general practitioner which, of course, produced no effect. This girl was subjected to the Frank-Geist "satchel-handle" operation and has a vagina about  $3\frac{1}{2}$  inches deep but lined with coarse skin bearing many hairs and secreting much sebaceous material. Unfortunately, her plans for marriage have not materialized.

CASE 2.—A woman of 22 years was engaged to be married and had had one unsuccessful operation in another city. When seen by me she had a very small

tortuous sinus leading from the perineum for several centimeters between the bladder and rectum. The Frank-Geist operation was done, the greatest difficulty being to create a cavity to which a tube graft could be applied as the scar from her former operation was extremely difficult to handle. A good graft was finally established but, much to my disgust, on removing the plug the entire graft came out. I then had her wear a  $\frac{7}{8}$ -inch test tube in the vagina constantly for four weeks and after that for a varying period of one-half to two or three hours a day. She has been married for several years, has perfect marital relationship and has a very pliable normal vagina.

CASE 3.—The third patient, 21 years of age had been married six months, but complained that intercourse had not been completely satisfactory. On examination she was found to have a definite pouch 2 inches deep between the rectum and bladder. On closer questioning I found that she had been attempting intercourse since she was 14 years old, which led me to conclude that the pouch had been produced by attempted intercourse over a long period of time. This patient consulted me only once and I do not know whether or not she has improved as time went on. I advised against any surgery.

CASE 4.—This case came to the clinic after one attempt had been made at another hospital with complete failure. This girl was mentally deficient and the Department of Charities and Social Workers were very much against having any more work done. With this plan I heartily agreed.

CASE 5.—This woman of 26 had never menstruated, but came with the statement that she was to be married in eight weeks. She was instructed in the use of Dr. Frank's method of gradual invagination by graded test tubes and she had a perfectly normal  $3\frac{1}{2}$  to 4 inch vagina at the end of seven weeks. When seen after her marriage she stated that her marital relationship was perfectly satisfactory.

CASE 6.—The next patient of the group was 50 years old and had been married 30 years. At the time I saw her she had two large pelvic tumors and the surgeon called me because he was unable to feel the cervix properly. A large mass was present in the right side of the pelvis which seemed to be a fibroid and another mass in the left inguinal canal extending to the labia. When I examined her, I found that she had no vagina but had created a deep pouch during her thirty years' marriage. When her abdomen was opened, it was found that she had a double uterus, each containing fibroids, the left uterus being incarcerated in the left inguinal canal. The two halves of the uterus were removed and no lumina were found.

CASE 7.—The next case was one of partial aplasia. This patient did not know there was anything wrong until after her marriage when she presented herself to her physician, pregnant. A diaphragm with only a small opening was discovered in the upper third of the vagina. By cesarean section she had two children. When I saw her she was rather nervous and apprehensive and complained of very unsatisfactory marital relationship. Two or three attempts had been made to establish a normal vaginal canal with rather poor success. The diaphragm was cut away and a glass plug was inserted and kept in place constantly for four weeks and then used about twice a day for about six weeks. The raw surface left by the incision of the diaphragm covered over nicely with epithelium and she now has a normal vagina with the cervix easily visible although somewhat shortened.

CASE 8.—The last case was one of true hermaphroditism. This girl of 11 had just started to menstruate but the blood apparently came through the urethra. Examination showed a normal appearing girl with developing breasts and normal pubic hair. In the left inguinal canal was a firm, tender mass the size of a small

time which seemed like a hernia but could not be reduced. She was advised to enter the hospital for study but before her hospitalization was effected the mass in the right groin became very painful and surgery seemed an immediate necessity. Incision of the inguinal canal revealed a black organ which looked like an ovary. This was removed and a hernial repair done. Sections of material removed, although somewhat distorted, resembled testicular tissue, and no evidence of ovarian structure was seen. She made an uneventful recovery but so far I have not been able to follow up her case to determine the complete picture of this congenital anomaly.

From my experience with these cases it seems evident that the more formidable operations can now be discarded. Case 2 indicates that practically no graft is necessary when the open operation is done. This corresponds very well with the experience of Meigs, Wharton and others, namely that if the canal is kept open with a nonirritating glass plug, epithelization will take place. I agree with Dr. Hobbs that we have no evidence to prove that the tissue put in these patients is actually the source of the epithelium which lines the canal. However, from my experience with the 3 patients who either by themselves or by test tubes produced vaginal canals by pressure, it seems this method is the simplest and will probably be the most universally used.

In closing I wish to say that I think any young woman so unfortunate as to be born without a vagina when she has the hope for marriage should have a vagina created.

DR. BENJAMIN P. WATSON, NEW YORK, N. Y.—I should like to report a successful case treated by the bloodless tube method. When the patient was 13 years old she had not menstruated and was having a great deal of periodic abdominal pain. Her doctor, thinking she had an imperforate hymen, made an incision, obtained nothing, and desisted from further attempts. She continued to have these periodic attacks of pain which ultimately became continuous. This was the stage at which I saw her.

On rectoabdominal examination one could make out a tense swelling to the left side of the pelvis and a tentative diagnosis of occluded double uterus was made. She had no vagina. It was found at operation that one horn was distended and occluded, the other quite small; both tubes and ovaries were perfectly normal. Both horns were removed and nothing more done. The girl was not told anything about the absence of the vagina at that time. When she was nearly 19 years old, she became interested in a young man and was determined that she was going to marry him. She had normal sexual reactions and normal secondary development. We began treatment by the Frank method. There was a small depression where the first incision had been made. She used larger and larger dilators and was very conscientious in their use. About ten months after the treatment was begun she was married and has now been married for about 1½ years. The marriage is perfectly happy and successful.

DR. ROBERT MEYER, MINNEAPOLIS, MINN.—In a critical review of the literature of hematocolpos, hematometra and hematosalpinx (1895) I pointed out that the occlusion in most cases was acquired by inflammatory processes presumably caused by infectious diseases of childhood.

The use of the term "aplasia of the vagina" means that it was never formed or strictly that it is a developmental anomaly. This can be caused by a primary defect of the lower end of the Müllerian ducts, either total or partial. The Müllerian epithelium can undergo regression soon after its early appearance in females as well as in intersexes, which is of course also the fate of the Müllerian ducts in most of their extent in males.



The vagina takes its origin from the Müllerian ducts only topographically, and not histologically. The Müllerian epithelium, after having built the vaginal canal, undergoes full regression and is replaced by the sinus epithelium which is of an entodermal nature. I can show you this in only a superficial way in a few photographs selected from more than 3,000.

I cannot omit mentioning that the hymen is formed by foldings of the vestibulum, the former entodermal sinus urogenitalis. An "imperforate hymen" cannot exist because it is open from the beginning. An occlusion must be the result of the growing together of the foldings at their margins. As a rule the so-called imperforate hymen is confused with a membrane-like atresia of the vaginal introitus.

When the Müllerian epithelium has not yet made contact with the sinus, the epithelium of the Müllerian vagina ripens to mucous epithelium as it does in the cervical canal. In fact in malformations, which one finds in newborn children and in cases of hematocolpos in the adults, the open or canalized part of the vagina is covered by mucous epithelium, as I found in some cases. If an excision of the occluding membrane is made, mucous epithelium will be found on the upper side as proof that the atresia is congenital.

Some locally persistent portions of Müllerian epithelium in the otherwise squamous epithelium-lined open vagina give rise to cysts, glands, and eventually adenomas and adenocarcinomas as in the cervix. In every case of congenital partial atresia of the vagina one should examine the mucosa to obtain information to aid in determining whether or not the Müllerian epithelium can change into squamous epithelium. Certainly one must be sure that in a double vagina if unilaterally occluded, the closed side does not communicate with the other normally developed side even through an opening in a cervical septum.

Finally I should like to raise the question of how the Müllerian epithelium in the vagina changes after the removal of the occluding membrane. One may ask not only if it becomes a squamous epithelium histologically but also how does it behave functionally? What is the content of glycogen; are there Doederlein bacilli; and are there cyclical changes? Do intestinal transplants act in the same or a similar way?

DR. NORMAN F. MILLER, ANN ARBOR, MICH.—I would like to raise a question in connection with this very interesting subject. It has been stated from time to time that "split thickness grafts" used in the reconstruction of artificial vaginas probably die and are replaced by epithelium from the vestibule or vulva. I am inclined to agree that this may occur but the point has not been proved.

We have been much interested in just what happened to the split thickness grafts and recently had occasion to study a patient in whom we had obtained a healthy take. The patient had complete absence of the vagina but did have tubes, uterus, and ovaries. At the time of admission she presented a hematometra and bilateral hematosalpinx. A channel was made and the accumulated blood drained off. Ten days later a split thickness skin graft was applied on an obturator which resulted in an excellent take. Three months later we studied this girl carefully and biopsies taken from the new vagina demonstrated typical vaginal epithelium. Whether this was a conversion of the transplanted epithelium into the vaginal type because of its new environment or whether the graft tissue had been replaced from the vestibule is something that further studies will have to determine.

DR. EMIL NOVAK, BALTIMORE, MD.—Like the previous speakers, I believe that the days of the more formidable procedures, such as the Baldwin operation, in the construction of an artificial vagina have passed. In former years I performed a number of these operations, and I still feel that the anatomic and functional results obtainable by this method surpass those following the employment

of the simpler and safer methods now in vogue. At the meeting of the American Association of Obstetricians and Gynecologists in Baltimore two years ago I showed the end results in one or two of these patients a good many years after operation, and I believe that those members who examined the patients agreed that the artificial canal could scarcely be distinguished from a normal vagina. However, in view of the magnitude of this operation and the inevitable element of risk, it has very properly been superseded by simpler methods which give very satisfactory if not always ideal results.

The particular point which I rose to discuss has already been touched upon by Dr. Meyer, to whom we are all indebted for his monumental researches in the embryology of the vagina. In certain cases of pseudohermaphroditism the vagina appears to be completely absent, while the urethra occupies essentially its normal position, often connected by a shallow furrow with the clitoris. By means of endoscopic studies and cystograms, however, the vaginal canal, often rather small and rudimentary, will be found to enter the urethra at an acute angle a short distance behind the meatus. In such cases it is possible by a very simple plastic procedure to open the vagina to the exterior, and the mistake of unnecessarily creating an artificial canal in the perineal body thus avoided. I have encountered two such cases in the past few years. The anomaly in these cases is an absence of the septum which subdivides the lower urogenital canal into an urethral and vaginal portion. It is easy to understand, therefore, that in such cases menstrual bleeding may occur from the urethra, and I believe that one of the cases reported by Dr. Sears will probably fall into this category.

DR. JOSEPH L. BAER, CHICAGO, ILL.—I have a report from a totally different category of a girl of 16, one of uniovular twins, the other being entirely normal. The patient presented herself with a pelvic mass of very considerable size, aplasia of the vagina and only a slight dimpling on the perineal surface. Through a transverse incision I tunneled down until what seemed to be the cervix was exposed. By probing I found the cervical canal and evacuated the huge retained menstrium.

Because of this patient's youth I had no desire to do an extensive tubular transplant, nor to begin the routine of glass tubes to maintain a vagina. Instead I anchored the cervix as close to the margins of the perineum as I could by heavy traction sutures, producing an artificial prolapse, if you please. This healed entirely, and five years after the operation she returned happily married. The vagina had constructed itself. Evidently the prolapsed uterus withdrew, the vulvar margin came up with it and she had an 8 cm. vagina.

DR. DANNREUTHER (closing).—I would like to make three points in commenting on the previous discussion. First, the results are much better, no matter what type of operation is done, if the surgical procedure is deferred until the patient plans to use the canal physiologically. Second, the hair on the inner aspect of the thigh seems to be a handicap in some candidates for the Frank-Geist operation, but I have overcome that by referring my patients to a dermatologist for removal of the hair by electrolysis. Third, it is easy to make frequent observations through the glass obturator and thus follow the process of epithelization in the new vaginal canal.

## A BACTERIOLOGIC STUDY OF PYOMETRA\*

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**P**YOMETRA is defined as an accumulation of pus within the uterus. The earliest recorded report of pyometra which we could find was "Case of a collection of pus in the cavity of an unimpregnated uterus," by J. Clarke<sup>1</sup> in 1812. This report was found in the first series of the index catalogue of the Library of the Surgeon's General Office. In this same series were found reports of either a collection of pus in the uterus, or a discharge of pus from the lining membrane of the uterus, by D. Schutte<sup>2</sup> in 1828, by Ashwell<sup>3</sup> in 1837, by Hyndman and Storer<sup>4</sup> in 1853, and by Taliaferro<sup>5</sup> in 1873. Undoubtedly there are earlier reports in the foreign and American literature.

Sporadic case reports of pyometra appeared in the literature of the late eighteen hundreds and in the early nineteen hundreds. There was a paucity of reports in the American literature.

In 1912, Loman<sup>6</sup> reviewed the literature and quoted the incidence of pyometra given by Sainclair, Berkle, Lewers, Tate, Lee and Bazy. He also discussed the causes, symptoms, classification, and pathology. His report was based on a study of patients with carcinoma of the cervix.

A review of the literature shows that pyometra was found commonly before radiation therapy was used clinically. After the advent of radiation therapy most case reports were of pyometra following the treatment of uterine cancer with radium and x-ray.

In 1915, Roberts<sup>7</sup> reported a patient in the postmenopausal age who had pyometra without carcinoma of the cervix or uterine corpus. In 1923, Lammers<sup>8</sup> reported pyometra in a patient treated by radium and x-ray for carcinoma of the cervix, and in that same year Alamanni<sup>9</sup> reported three patients with carcinoma of the cervix, for which no radiation or operative therapy was used, in whom pyometra developed. In 1924, Condamin<sup>10</sup> reported pyometra in a patient with carcinoma of the cervix treated with radium and x-ray. In 1927, Violet<sup>11</sup> found pyometra at hysterectomy in a woman of 65 years with carcinoma of the corpus of the uterus. In 1927, Esser<sup>12</sup> reported an operation upon a woman of 60 years with carcinoma of the vagina, cervix, and uterus; 2,000 c.c. of pus were found in the vagina, cervix, and uterus. In 1928, Reeb<sup>13</sup> reported the finding of a calcified concretion, or uterine stone, blocking the cervix with resultant pyometra in a woman of 77 who had had at the age of 44 a dilatation and curettage and radium therapy for a small fibroid of the uterus. In the same year Guyot, Jeanneney, and Varrin<sup>14</sup> described pyometra and hematometra in a patient with carcinoma of the cervix, before and after radiation ther-

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apy. Stacy,<sup>15</sup> in 1928, in discussing the complications of radium therapy to pelvic lesions, did not report pyometra specifically but mentioned it in his discussion. In 1929, Godlewski<sup>16</sup> reported pyometra in a woman of 30 years who was operated upon for a twisted, infected dermoid cyst and who, one year previously, had had acute gonorrheal cervicitis and salpingo-oophoritis for which she had received vaccine therapy. Pride<sup>17</sup> in that same year gave a report of a patient of 28 with a submucous fibroid, but with no cervical stenosis, in whose uterine wall was found an abscess containing 500 c.c. of pus.

In 1929, Bland<sup>18</sup> reported pyometra in three patients who previously had received radium therapy for uterine cancer. His article reviewed the etiology, classification, symptoms, prognosis, and treatment in pyometra. Middleton,<sup>19</sup> in 1931, published his report of pyometra in a pseudohermaphrodite. The pyometra was first drained and later the uterus was removed. Remmelts<sup>20</sup> in the same year reported pyometra in a woman of 43 years with carcinoma of the cervix who had received no radium or x-ray therapy. In 1932, Guilhem and Gouzy<sup>21</sup> reviewed the subject of pyometra in carcinoma of the cervix after radium therapy and discussed the predisposing causes, the pathology, the clinical forms, and the preventive and the curative treatment. They emphasized the fact that infection was present in all cervixes with carcinoma and stated that the streptococcus was always present, but was rarely hemolytic, and, therefore was less virulent. Liegner,<sup>22</sup> in 1930, described a diabetic, aged 57 years, who had a small submucous fibroid and stricture of the vagina with retention of pus in the vagina and uterus. She had no cancer. Barrows,<sup>23</sup> in 1934, listed pyometra of the cervical stump in a patient who previously had had performed bilateral salpingo-oophorectomy and supravaginal hysterectomy. In 1934, Hirsch<sup>24</sup> reported pyometra in a patient who had adenocarcinoma of the corpus of the uterus and who eight years previously had received radium therapy for carcinoma of the cervix. Gemmill,<sup>25</sup> in 1934, reported pyometra, with 600 c.c. of pus in the uterus, in a patient who was pregnant three or four months.

Massbuaud and his group<sup>26</sup> in 1935 reported a woman of 64 years, who had received radium therapy five years previously for carcinoma of the cervix, and who developed carcinoma of the corpus of the uterus with pyometra. In 1936, Szathmary<sup>27</sup> found pyometra in the uterus of a woman of 63 years who also had granulosal cell tumor of the ovary.

Weinstein, Gardner, and Allen,<sup>28</sup> in 1937, attempted to show that the injection of estrogenic substance in mice tended to produce pyometra. Bacteria were present in higher percentages in the uteri of the mice which received the hormone than in the uteri of a control group of mice. In 1938, Grenier<sup>29</sup> reported pyometra in five patients after radium therapy for carcinoma of the cervix. Carriere, Gineseste, and Devos,<sup>30</sup> in 1938, reported a patient of 64 years who had no carcinoma but who developed peritonitis from spontaneous rupture of a pyometra. Smears from the pus showed mixed organisms but full bacteriologic studies were not done.

In 1939, Loranger<sup>31</sup> reported a patient of 22 years with a sterile pyometra who previously had received numerous injections of estrogenic substance. He quoted the experimental use of estrogens to produce pyometra in mice and theorized that estrogenic substance might produce pyometra. Graham and Failla,<sup>32</sup> in 1940, found a spontaneous occlusive pyometra in a woman of 73 years who had no carcinoma.

Smears from the pus were positive for gram-negative intracellular diplococci and mixed organisms. Cultures were reported positive for mixed organisms, but it was not stated that the gonococcus was found.

#### PATHOLOGY

Certain predisposing pathologic conditions antedate the formation of true pyometra. Loman<sup>6</sup> stated that normally the uterine secretion was small in amount and free of bacteria and that the physiologic function of the cervical secretions and coverings was the destruction of bacteria. In cancer of the cervix the resultant circulatory disturbances favored infection. He quoted Bazy who claimed that cancer of the cervix was limited to the lower part of the cervical canal. The mucous membrane of the canal above the cancer growth was ulcerated and covered with pus. Swelling, due to capillary and lymphatic dilatation, occurred. Bazy considered this process one of inflammation of the cervical canal with sclerosis and lymphangitis. Loman gave as causes of pyometra new growths which constricted the cervix, atresia due to the sclerotic atrophy which occurred after menopause, and a cancerous swelling which acted as a valve by forcing itself into the cervical canal.

Bland<sup>18</sup> listed as possible causes of pyometra any condition which causes partial or complete obstruction of the cervical canal, inflammatory edema about the cervical os, senile fibrosis, endometrial vegetations and polyps, myomas, chemical ulceration followed by fibrosis, malpositions of the uterine body and congenital gynatresia. His article stressed postirradiation pyometra and emphasized the fact that radium converted neoplastic tissue to dense fibrous tissue which in turn contracted and caused fusion of the walls of the cervix. The fluid accumulation in the uterine cavity resulted from associated inflammatory changes in the endometrium and the myometrium, lesions almost invariable accompaniments of cervical carcinoma. That the fluid accumulation was inflammatory in origin was predicated upon the observation that the normal secretion of the endometrium was practically nil. Since the cancer tissue contained all forms of pathogenic bacteria, the fluid in the uterine cavity was readily infected.

Guilhem and Gouzy<sup>21</sup> discussed pyometra after radium therapy in cancer of the cervix and gave as a predisposing cause the inability of the uterine secretions to escape through the os. Radium therapy modified the distribution of the tubular glands in the mucous membrane of the uterus and insufficient radium dosage and incorrect intracervical application caused some glands to be destroyed whereas other glands continue to secrete. They also claimed that infection of cervical cancer always occurred and that streptococci were always found in the cancer tissue. The streptococci found were rarely hemolytic and as a result were less virulent. Since bacteria were present before, during, and after treatment, increased uterine secretion resulted not only from the presence of infection but also from the tissue destruction which radium caused. This tissue destruction itself caused increased secretions. Other pathologic lesions of the cervix caused uterine secretions to be retained. Due to the degeneration of the muscular wall of the uterus following radiation therapy with the loss of uterine contractility, and to the cervical stenosis, distention of the uterine cavity occurred. The true determining causes of pyometra were due to the radiation sclerosis of the cervix with partial or complete stenosis. In postirradia-

tion pyometra they described the anatomic pathology as follows: the cervix reduced to a stump with the vaginal portion deformed or destroyed; the uterine wall thickened; the uterine mucosa purple or grayish in color; the endometrium the site of the endometritis; interstitial metritis later with ulceration; inflammation around the uterus with adnexal lesions and adhesions; varying quantities of pus of different colors in the uterine cavity.

#### BACTERIOLOGY

The importance of infection, in the predisposing pathologic conditions antedating the formation of pyometra, was stressed in the foregoing reviews of the pathology. No studies of the bacteriologic findings in pyometra could be found since anaerobic cultural methods have been proved to be of fundamental importance in the study of pelvic infections. The routine use of these culture methods has changed our concept of pelvic infection so markedly that it seemed logical to study the bacteriology of pyometra by complete anaerobic and aerobic cultures.

Bacteriologic studies in our clinic of the cavities of large myomatous uteri removed in the childbearing age and of the cavities of small senile uteri removed by vaginal hysterectomy in descensus and procidentia had shown that the cavities in these uteri were sterile if rigid technique were used in the method of culture.

#### MATERIAL

Complete aerobic and anaerobic cultures of the pus from 39 patients with pyometra were done. Aerobic cultures were done of the pus from 6 patients with pyometra, and no cultures were obtained from 3 patients. The high incidence of anaerobic organisms in pelvic infection made incomplete the studies in which only aerobic cultures were done.

*Collection of Material.*—In the collection of the pus for culture, the possibility of vaginal and cervical contamination could not be entirely excluded. Routine precautions prior to culture to prevent contamination included the washing of the vagina and cervix with green soap and alcohol. This preparation of the vagina and cervix was used prior to the sounding of the cervixes and uteri of all senile patients, of all patients who had operations upon the cervix and of all patients who had been or were to be treated by irradiation therapy. When sounding of the cervix was indicated in the childbearing age due attention was given to the menstrual history of the patient, and in many patients, pregnancy tests were done prior to the sounding of the cervix and uterus.

After the cervix had been dilated by a sound, or by a probe, a very small metal cannula was passed into the uterine cavity. In most patients the amount of pus present in the cavity was sufficient to make possible cultures without obvious contamination.

An important check on the method of collection was a routine examination of smears, prior to culture. In a majority of the patients the results of cultures confirmed the findings of the smears made of the pus.

*Culture Methods.*—For the growth of aerobic organisms the pus was streaked directly on beef infusions, sheep's blood agar plates. For anaerobic plate culture the same medium was used, but the plates were placed in anaerobic jars and a slight modification of the hydrogen replacement method, as described by McIntosh and Fildes,<sup>33</sup> was used.

TABLE I. PYOMETRA COMPLICATING SQUAMOUS CELL CARCINOMA OF THE CERVIX (NO PREVIOUS RADIATION OR OPERATIONS) (12 CASES)

| HIST. NO.<br>RACE—AGE<br>PARTY | CLINICAL SYMPTOMS                      |      |       |                   | ASSOCIATED<br>DISEASES                                  | OPERATIVE<br>FINDINGS<br>(C.C. PUS) | BACTERIOLOGIC<br>FINDINGS         | FOLLOW UP |
|--------------------------------|--|------|-------|-------------------|---|-------------------------------------|-----------------------------------|-----------|
|                                | VAGINAL BLEED-<br>ING AND<br>DISCHARGE | PAIN | FEVER | LEUCO-<br>CYTOSIS |   |                                     |                                   |           |
| 86155<br>W—54 yr.<br>11-0-9    | +                                      | -    | -     | -                 | Carcinoma, nose   | 1500                                | No growth                         | Living    |
| 79772<br>W—69 yr.<br>12-0-1    | +                                      | +    | -     | -                 | Senile vag. dysuria                                     | 40                                  | No growth (aero-<br>bic only)     | Living    |
| 64878<br>W—52 yr.<br>16-2-12   | +                                      | +    | +     | +                 | Pyelitis—Cystitis;<br>R.V.O., small cys-<br>toretocoele | 10                                  | Not done                          | 0         |
| 66739<br>C—44 yr.<br>13-1-9    | +                                      | -    | +     | +                 | Redundant vagina,<br>dysuria                            | 300                                 | Strep. viridans<br>(aerobic only) | 0         |
| 58905<br>W—50 yr.<br>13-0-1    | +                                      | +    | -     | -                 | Vaginitis   | 10                                  | Staph. aureus<br>(aerobic only)   | 0         |
| 91771<br>W—52 yr.<br>2-0-2     | +                                      | +    | -     | -                 | Stricture of ureter                                     | 30                                  | No growth                         | Living    |

Evaluation of these cases disclosed the following diagnosis:

|                                |       |
|--------------------------------|-------|
| Senile vaginitis and kraurosis | 9     |
| Leucoplakia                    | 7     |
| Dermatitis venenata            | 1     |
| Lichen simplex chronicus       | 1     |
| Monilia infection              | 1     |
| Diabetes mellitus              | 2     |
|                                | <hr/> |
|                                | 21    |

Those cases diagnosed as senile vaginitis, kraurosis and leucoplakia were treated. The rest were referred to appropriate clinics for further investigation.

The treatment consisted of the local application of an ointment of lanolin base containing 10 mg. of diethylstilbestrol per 30 c.c. of salve. The patients were instructed to apply about 30 c.c. of the ointment locally every day for one week. It is obvious that this could result in only an approximate daily dosage of estrogen. If improvement occurred at all, it was usually quite apparent within one week, but the treatment was tried for one month in the unimproved cases before being given up as unsuccessful. The success or failure of the treatment was based entirely on its ability to relieve the symptoms of pruritus and burning. No biopsies were made of vaginal or vulvar tissue.

Of the 9 patients in the senile vaginitis, kraurosis group, 5 were completely relieved of symptoms, 1 was improved, and 2 were unimproved. One was not treated with estrogen salve because of the presence of carcinoma elsewhere in the body.

Of the 7 patients with leucoplakia, 2 were completely relieved, 1 was improved, and 4 were unimproved.

Three of the above 16 patients have remained symptom free without further treatment after one month of inunction. The others find it necessary to resort to the use of salve once or twice a week to prevent recurrence of symptoms.

Several patients obtained relief from coincidental hot flushes during treatment, and one patient had a period of uterine bleeding following cessation of treatment. These cases indicate a systemic reaction to estrogen absorbed percutaneously, and the uterine bleeding was thought to be an estrogen withdrawal phenomenon.

#### SUMMARY

Kraurosis vulvae and leucoplakia are causes of pruritus vulvae. The differences in their distribution and pathology are discussed.

Since kraurosis is more closely akin to senile vaginitis and therefore may be due to estrogen depletion, it was thought that kraurosis might be more susceptible to estrogen therapy than leucoplakia.

Twenty-one patients complaining of pruritus vulvae are reviewed.



TABLE II. PYOMETRA COMPLICATING SQUAMOUS CELL CARCINOMA OF THE CERVIX (WITH PREVIOUS RADIATION OR PREVIOUS OPERATIONS)  
(12 CASES)

| HIST. NO.<br>RACE—AGE<br>PARITY | CLINICAL SYMPTOMS                         |      |       |                   | ASSOCIATED<br>DISEASES                         | OPERA-<br>TIVE<br>FINDINGS<br>(C.C.<br>PUS) | BACTERIOLOGIC<br>FINDINGS                             | PREVIOUS<br>RADIATION | TYPE OF<br>PREVIOUS<br>OPERATIONS                          | FOLLOW UP |
|---------------------------------|---|------|-------|-------------------|--|---|---|-----------------------|--|-----------|
|                                 | VAGINAL<br>BLEEDING<br>AND DIS-<br>CHARGE | PAIN | FEVER | LEUCO-<br>CYTOSIS |  |   |   |                       |  |           |
| 93237<br>W—62 yr.<br>1-0-1      | +   | +    | -     | -                 | Bromidism<br>atrophic ext.<br>genitals         | 10  | No growth   | -                     | Numerous dila-<br>tations and<br>curettages                | 0         |
| 75644<br>W—51 yr.<br>5-0-5      | +   | +    | -     | -                 | -  | 40  | Not done  | X-ray<br>Radium       | Radium intra-<br>cervical                                  | Living    |
| 79312<br>W—59 yr.<br>8-0-6      | +   | -    | -     | +                 | Chr. cervitis &<br>cervical adhe-<br>sions     | 50  | No growth   | X-ray                 | -  | 0         |
| 17238<br>W—71 yr.<br>4-0-3      | +   | +    | +     | -                 | Senility fre-<br>quency                        | 20  | E. coli commun.<br>anaerobic cocci,<br>diph. bacillus | X-ray<br>Radium       | Radium intra-<br>cervical                                  | Living    |
| A18074<br>W—51 yr.<br>5-0-4     | +   | +    | -     | -                 | 0  | 20  | Mixed anaerobes<br>diph. bacillus                     | Radium                | Radium intra-<br>cervical                                  | Living    |
| A13493<br>C—69 yr.<br>1-1-0     | +   | -    | -     | -                 | Atrophic ext.<br>genitals, va-<br>gina, cervix | 30  | Mixed anaerobes<br>staph. albus<br>diph. bacillus     | Radium<br>X-ray       | Dilatation and<br>curettage ra-<br>dium intra-<br>cervical | 0         |

|  |                                   |                        |                         |                                     |   |     |   |                               |
|--|-----------------------------------|------------------------|-------------------------|-------------------------------------|---|-----|---|-------------------------------|
| A16883<br>W—56 yr.<br>8-1-7                          | +                                 | —                      | +                       | —                                   | Obesity   | 20  | Anaerobic strep.<br>strep. gamma  | Living                        |
| 97246<br>W—80 yr.<br>5-0-4                           | +                                 | +                      | —                       | —                                   | —   | 10  | Diph. bacillus  | 0                             |
| A55553<br>W—53 yr.<br>4-0-4                          | +                                 | —                      | +                       | +                                   | Lac. perineum con-<br>striction upper<br>vagina | 150 | Mixed anaerobes   | 0                             |
| A42183<br>W—65 yr.<br>9-0-5                          | +                                 | +                      | +                       | —                                   | Senile vaginal and<br>vulval changes            | 200 | Mixed anaerobes   | 0                             |
| A63108<br>W—69 yr.<br>8-1-7                          | +                                 | —                      | —                       | —                                   | Atrophic changes<br>genitalia                   | 75  | Anaerobic cocci   | Living                        |
| A48530<br>W—56 yr.<br>0-0-0                          | +                                 | +                      | —                       | —                                   | Obesity   | 100 | Staph. aureus   | Living                        |
| Postmeno. 12<br>Nullip. 1<br>Multip. 11<br>W—11, C—1 | Bleeding<br>12<br>Discharge<br>12 | Pain<br>7<br>Neg.<br>5 | Fever<br>5<br>Neg.<br>7 | Leuco-<br>cytosis<br>3<br>Neg.<br>9 |   |     | Culture—11<br>Not done—1<br>Anaerobes—3<br>Aerobes—4<br>Mixed—1<br>Neg.—3 | Living—6<br>Not followed<br>6 |

TABLE III. PYOMETRA COMPLICATING ADENOCARCINOMA OF THE UTERUS (5 CASES)

| HIST. NO.<br>RACE-AGE<br>PARITY                    | CLINICAL SYMPTOMS                         |                        |                         |                          | ASSOCIATED<br>DISEASES   | OPERA-<br>TIVE<br>FINDINGS<br>(C.C.<br>PUS) | BACTERIOLOGIC<br>FINDINGS                    | PREVIOUS<br>RADIATION | TYPE OF<br>PREVIOUS<br>OPERATION                          | FOLLOW UP          |
|--|---|------------------------|-------------------------|--------------------------|--|---|--|-----------------------|---|--------------------|
|  | VAGINAL<br>BLEEDING<br>AND DIS-<br>CHARGE | PAIN                   | FEVER                   | LEUCO-<br>CYTOSIS        |  |   |  |                       |   |                    |
| 47477<br>W-65 yr.<br>1-0-1                         | +   | +                      | -                       | -                        | Cystitis senile va-<br>ginitis   | 50  | No growth                                    | X-ray                 | Dilatation and<br>curettage                               | Living             |
| A42196<br>W-80 yr.<br>0-0-0                        | +   | -                      | -                       | -                        | Stenosed upper va-<br>gina, retroverted<br>uterus, senile<br>genital changes | 150   | No growth                                    | -                     | Dilatation and<br>curettage                               | Living             |
| 93092<br>W-55 yr.<br>6-1-5                         | +   | +                      | +                       | +                        | Senility, atrophic<br>arthritis, anemia,<br>abdominal ascites                | 200   | Anaerobic mixed<br>organisms strep.<br>gamma | Rad.                  | Radium intra-<br>uterine                                  | Died               |
| 74666<br>W-56 yr.<br>5-0-2                         | +   | +                      | -                       | -                        | Atrophic external<br>genitals  | 20  | No growth                                    | Rad.                  | Uterus packed<br>radium intra-<br>uterine                 | Died               |
| A78440<br>W-54 yr.<br>9-0-6                        | +   | -                      | -                       | -                        | Obesity, ureteral<br>stricture   | 150   | Anaerobic cocci                              | Rad. and<br>x-ray     | Dilatation and<br>curettage ra-<br>dium intra-<br>uterine | Living             |
| Postmeno. 5<br>Nullip. 1<br>Multip. 4<br>W-5; C. 0 | Bleeding<br>5<br>Dis-<br>charge<br>5      | Pain<br>3<br>Neg.<br>2 | Fever<br>1<br>Neg.<br>4 | Leuco.<br>1<br>Neg.<br>4 | .  |   | Negative<br>Anaerobic<br>Mixed               | X-ray 2<br>Radium 3   | Dilatation and<br>curettage 3<br>Radium 3<br>Ut. packed 1 | Living 3<br>Died 3 |

|  |  |                        |                         |                                      |                                    |    |   |                            |  |   |
|--|--|------------------------|-------------------------|--------------------------------------|------------------------------------|----|---|----------------------------|--|---|
| A29684<br>W—26 yr.<br>2-0-2                              | +                                      | +                      | -                       | -                                    | 0                                  | 10 | Anaerobic cocci   | X-ray                      | -  | Died                                    |
| A33662<br>W—66 yr.<br>11-4-7                             | +                                      | -                      | -                       | -                                    | R.V.O.                             | 8  | No growth   | X-ray                      | -  | Died                                    |
| A53429<br>W—38 yr.<br>6-0-3                              | +                                      | +                      | -                       | +                                    | Papilloma of<br>vagina             | 25 | Anaerobic cocci,<br>staph. albus,<br>strep. hem.,<br>grp. B | X-ray<br>Radium            | Dilatation and<br>curettage,<br>conization<br>cervical, ra-<br>dium intra-<br>cervical | Living                                  |
| A45035<br>W—43 yr.<br>3-0-3                              | +                                      | -                      | +                       | -                                    | -                                  | 20 | Anaerobic cocci   | X-ray<br>Radium            | Radium intra-<br>cervical  | Died                                    |
| A35199<br>W—44 yr.<br>5-1-3                              | +                                      | -                      | +                       | -                                    | -                                  | 20 | Strep. viridans<br>diph. bacillus                           | X-ray<br>Radium            | Radium intra-<br>cervical  | Living                                  |
| A72755<br>W—54 yr.<br>12-2-7                             | +                                      | +                      | -                       | -                                    | R.V.O.<br>Senile ehgs.<br>genitals | 10 | Anaerobic cocci   | X-ray                      | -  | Living                                  |
| Multip. 12<br>W. 11<br>C. 12<br>Postmeno. 7<br>Menstr. 5 | Bleeding<br>12<br>Dis-<br>charge<br>12 | Pain<br>7<br>Neg.<br>5 | Fever<br>3<br>Neg.<br>9 | Leuco-<br>cytosis<br>2<br>Neg.<br>10 |                                    |    | Not done—1<br>Neg.—3<br>Anaerobes—3<br>Aerobes—1<br>Mixed—4 | X-ray<br>10<br>Radium<br>7 | Dilatation and<br>curettage—3<br>Intracervical<br>radium—7<br>Conization—1             | Living 6<br>Died 3<br>No follow<br>up 3 |

TABLE V. SPONTANEOUS PYOMETRA (NO CARCINOMA, PREVIOUS OPERATIONS OR RADIATION THERAPY) (15 CASES)

| HIST. NO.<br>RACE--AGE<br>PARITY | CLINICAL SYMPTOMS   |                      |      |       |                   | ASSOCIATED<br>DISEASES                                | OPERATIVE<br>FINDINGS<br>(C.C. PUS) | BACTERIOLOGIC<br>FINDINGS                   | FOLLOW<br>UP |
|----------------------------------|---------------------|----------------------|------|-------|-------------------|---|-------------------------------------|---|--------------|
|                                  | VAGINAL<br>BLEEDING | VAGINAL<br>DISCHARGE | PAIN | FEVER | LEUCO-<br>CYTOSIS |   |                                     |   |              |
| 71172<br>W-60 Yr.<br>0-0-0       | +                   | +                    | +    | -     | -                 | Senile vaginitis,<br>Strict. vagina,<br>Myomat. uteri | 8                                   | Bacillus pyo-<br>cyanus                     | 0            |
| 17238<br>W-53 Yr.<br>8-1-7       | -                   | +                    | +    | -     | -                 | Minimal<br>cervicitis                                 | 5                                   | Mixed anaerobic<br>cocci, piph.<br>bacillus | Well         |
| 96900<br>W-55 Yr.<br>11-0-9      | -                   | +                    | +    | -     | -                 | Pyelitis,<br>Cystitis,<br>Urethritis                  | 50                                  | Streptococcus<br>hemolyticus,<br>grp. B.    | Well         |
| 82254<br>W-60 Yr.<br>0-0-0       | -                   | +                    | +    | +     | +                 | Senile vaginitis<br>; constriction<br>Rheumatism      | 25                                  | Not done                                    | Well         |
| 75802<br>W-65 Yr.<br>8-2-7       | +                   | +                    | -    | -     | -                 | Atrophic ext.<br>genitals, vagina<br>& cervix         | 40                                  | No growth<br>(aerobic only)                 | Well         |
| 80258<br>C-54 Yr.<br>13-2-11     | -                   | +                    | -    | -     | -                 | Cervicitis &<br>Atrophy                               | 40                                  | No growth<br>(aerobic only)                 | 0            |
| 59360<br>W-57 Yr.<br>0-0-0       | -                   | +                    | -    | -     | -                 | Senile genitals                                       | 10                                  | E. coli<br>communior                        | Well         |
| 88789<br>W-74 Yr.<br>11-1-8      | -                   | +                    | +    | +     | +                 | Vaginitis   | 100                                 | Anaerobic<br>cocci                          | Well         |

TABLE IV. PYOMETRA (FOLLOWING CERVICAL OR UTERINE OPERATIONS) (4 CASES)

| HIST. NO.<br>RACE—AGE<br>PARITY                   | CLINICAL SYMPTOMS                     |                        |                         |                                     | ASSOCIATED<br>DISEASES   | OPERATIVE<br>FINDINGS<br>(C.C. PUS) | BACTERIO-<br>LOGIC<br>FINDINGS         | TYPE OF<br>OPERATIONS<br>(PREVIOUS)                         | FOLLOW<br>UP   |
|---|---------------------------------------|------------------------|-------------------------|-------------------------------------|--|-------------------------------------|--|---|----------------|
|   | VAGINAL<br>BLEEDING AND<br>DISCHARGE  | PAIN                   | FEVER                   | LEUCO-<br>CYTOSIS                   |  |                                     |  |   |                |
| 11191<br>W—52 yr.<br>11-0-9                       | +<br>↓<br>+                           | -                      | -                       | -                                   | Laceration of peri-<br>neum; cystocele;<br>rectocele chr. cervi-<br>citis; Lac. cervix             | 30                                  | No growth<br>aerobic only              | Dilatation and<br>curettage                                 | Well           |
| 94816<br>W—51 yr.<br>9-3-1                        | -<br>+                                | -                      | -                       | -                                   | Cystocele, rectocele   | 50                                  | Strep. viri-<br>dans diph.<br>bacillus | Removal of cervi-<br>cal polyp, repair<br>3° laceration     | Well           |
| A13493<br>W—47 yr.<br>6-1-4                       | -<br>+                                | +                      | -                       | -                                   | Endocervicitis, menor-<br>rhagia, trichomoniasis,<br>stenosis of cer-<br>vix.                      | 10                                  | Anaerobic<br>cocci                     | Cauterization of<br>cervix                                  | Well           |
| A4111<br>W—44 yr.<br>9-5-3                        | -<br>+                                | +                      | +                       | +                                   | Perineal tear, R.V.O.,<br>2 small cystocele and<br>rectocele, sl. cervi-<br>citis, pruritus vulvae | 25                                  | Anaerobic<br>cocci                     | Cauterization of<br>cervix                                  | Well           |
| Postmeno-<br>pausal<br>Menstr.<br>Multip. 4; W. 4 | Bleeding<br>Neg.<br>Discharge<br>Neg. | Pain<br>2<br>Neg.<br>2 | Fever<br>1<br>Neg.<br>3 | Leuco-<br>cytosis<br>1<br>Neg.<br>3 |  |                                     | Aerobes<br>Anaerobes 2                 | Dilatation and<br>curettage<br>Caut'r.<br>Removal<br>polyps | Well<br>4<br>1 |

For broth culture of the anaerobes a medium using neutralized beef heart as described by Lepper and Martin<sup>34</sup> was found most satisfactory.

*Clinical Grouping of Patients.*—Tables I to V show our clinical grouping of the patients.

*Bacteriologic Findings.*—The complete cultural findings in the pus from 39 patients with pyometra are shown in Table VI. Cultures of the pus from 8 patients showed no growth. Sterile cultures from pyometra were most common in patients with adenocarcinoma of the uterine corpus. No culture was sterile in the "spontaneous" group with pyometra.

TABLE VI

|   | MIXED<br>ANAEROBIC<br>COCCI | MIXED AN-<br>AEROBIC COCCI<br>AND ANAEROBIC<br>BACILLI<br>(NO SPORES) | MIXED<br>AEROBIC AND<br>ANAEROBIC<br>ORGANISMS | AEROBIC<br>ORGANISMS | NO<br>GROWTH |
|---|-----------------------------|---|--|----------------------|--------------|
| Spontaneous<br>pyometra<br>(no carcinoma,<br>previous radiation<br>or operations)                 | 5                           | 0   | 2  | 5                    | 0            |
| Pyometra<br>(following<br>operations on the<br>cervix uteri)                                      | 2                           | 0   | 0  | 1                    | 0            |
| Pyometra<br>complicating<br>carcinoma of<br>cervix<br>(no previous<br>radiation or<br>operations) | 1                           | 2   | 1  | 2                    | 2            |
| Pyometra<br>complicating<br>carcinoma of<br>cervix<br>(previous<br>radiation or<br>operations)    | 3                           | 0   | 4  | 1                    | 3            |
| Pyometra<br>complicating<br>adenocarcinoma of<br>uterus   | 1                           | 0   | 1  | 0                    | 3            |
| Totals  | 12                          | 2   | 8  | 9                    | 8            |

## DISCUSSION OF BACTERIOLOGIC FINDINGS

*Anaerobic Infection.*—Early in this study attempts were made to group the various strains of anaerobic cocci by the method advocated by Colebrook,<sup>35</sup> who used colony formation as a basis for grouping. It was found that a grouping of this type was unsatisfactory. Pure culture studies showed that the term "anaerobic streptococci" for the group as a whole was a poor one. Morphologically, many strains resembled more closely staphylococci. Growth was easily obtained in the mixed cultures or in symbiosis. Separation and propagation of *individual*

|   |                          |                           |                        |                          |                                      |  |    |   |                              |
|---|--------------------------|---------------------------|------------------------|--------------------------|--------------------------------------|--|----|---|------------------------------|
| 37050<br>W—70 Yr.<br>6-0-6  | +                        | +                         | -                      | -                        | -                                    | Cystocele<br>Rectocele, decensus<br>uteri                  | 20 | Streptococcus<br>hemolyticus,<br>grp. A   | Well                         |
| A60223<br>W—71 Yr.<br>7-2-7                                       | -                        | +                         | +                      | -                        | +                                    | Senility<br>Arthritis rt.<br>shoulder                      | 10 | Strep. viridans<br>Strep. gamma           | 0                            |
| A63429<br>W—57 Yr.<br>9-0-8                                       | +                        | +                         | -                      | -                        | -                                    | Acute cervicitis   | 15 | Anaerobic cocci                           | 0                            |
| A71408<br>C—62 Yr.<br>11-0-6                                      | +                        | +                         | +                      | +                        | -                                    | Senile genitals  | 15 | Anaerobic cocci                           | Well                         |
| A29684<br>C—55 Yr.<br>1-1-0                                       | +                        | +                         | +                      | -                        | -                                    | Senile genitals  | 20 | Anaerobic cocci                           | 0                            |
| A51870<br>W—42 Yr.<br>13-2-7                                      | +                        | +                         | -                      | -                        | -                                    | Completely<br>stenosed cervix<br>Nursing 18 mos.<br>infant | 20 | Anaerobic cocci                           | Well                         |
| A83632<br>C—55 Yr.<br>0-0-0                                       | -                        | -                         | -                      | -                        | -                                    | Completely<br>stenosed<br>cervix                           | 10 | Anaerobic cocci                           | Well                         |
| Postmeno.—14<br>Menstr.—1<br>Nullip.—4<br>Multip.—11<br>W—11; C—4 | Bleeding 7<br>Negative 8 | Discharge<br>14<br>Neg. 1 | Pain<br>8<br>Neg.<br>7 | Fever<br>3<br>Neg.<br>12 | Leuco-<br>cytosis<br>3<br>Neg.<br>12 |  |    | Not done<br>Anaerobic<br>Aerobic<br>Mixed | Well—10<br>Not<br>Followed 5 |



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## DISCUSSION

DR. HARVEY B. MATTHEWS, BROOKLYN, N. Y.—At the Long Island College Hospital we have encountered pyometra 25 times in the past seventeen years. The records of three patients were not available and hence this report will include only 22 cases. Dr. Carter's grouping is excellent, and we have used it in collecting our data. There are 5 groups as follows:

|   |                |
|---|----------------|
| 1. Pyometra complicating squamous cell cancer of cervix (no previous operations or radiation)   | NO. CASES<br>0 |
| 2. Pyometra complicating squamous cell cancer of cervix (with previous radiation or operation)  | 6              |
| 3. Pyometra complicating adenocarcinoma of the uterus (without previous radiation or operation) | 2              |
| 4. Pyometra following cervical or uterine operations  | 6              |
| 5. "Spontaneous" pyometra (no carcinoma, previous operation or radiation therapy)               | 8              |
| Total cases   | 22             |

strains were more difficult and often impossible. We feel that much further work must be done on methods of culture within this group before any method of classification of the group as a whole has practical significance.

The term "anaerobic" as used means obligate anaerobiosis. All microaerophilic strains, or strains which grew aerobically after several transplants, were classed as aerobes. The term "anaerobic cocci" means in general a mixture of cocci, streptococci, and diplococci. The term "mixed anaerobes" means that with the cocci were mixed various types of anaerobic nonspore-forming bacilli.

In 39 complete cultures anaerobic organisms were found in 22. In 12 cultures anaerobic cocci were found alone; in 2 cultures they were found with anaerobic bacilli; in 8 cultures they were in symbiosis with aerobic organisms.

*Aerobic Infection:* Purely aerobic organisms were found in 9 cultures. In 8 other cultures they were found in symbiosis with anaerobic organisms.

*Streptococcus hemolyticus* (Group B, Lancefield) was isolated twice, once in pure culture and once in symbiosis with *Staphylococcus albus* and with anaerobic cocci. *Streptococcus hemolyticus* (Group A, Lancefield) was isolated once in pure culture.

*E. coli communior* was isolated once in pure culture and *E. coli communis* once in symbiosis with anaerobic cocci and with a diphtheroid bacillus.

Diphtheroid bacilli were found 9 times in symbiosis and once in pure culture.

Aerobic nonhemolytic streptococci were found 3 times in symbiosis with other organisms.

*Streptococcus viridans* was found in symbiosis in 3 cultures.

*Staphylococcus aureus* was found once in pure culture and twice in symbiosis with other organisms.

Bacillus pyocyaneus was isolated once in pure culture.

#### CONCLUSIONS

From analysis of this small series no definite conclusions can be drawn. Since anaerobic organisms, capable of invading the cervix and uterine cavity are found normally in the vaginas of postmenopausal women in a higher incidence than in the vaginas of childbearing women, the possibility of endogenous infection must be considered. When nonhemolytic streptococci, diphtheroid bacilli, *Streptococcus viridans*, *Staphylococcus albus*, and bacilli of the colon group are cultured in pyometra, endogenous infection may be predicated. On the other hand the culture of *Streptococcus hemolyticus* (especially Group A) and *Staphylococcus aureus*, neither of which is commonly found in the vagina, argues against endogenous infection.

Whether infection is necessary in the production of "spontaneous" and "operative" pyometra can only be determined by careful culture of a large number of pyometra patients. In this small series sterile pyometra occurred most commonly in uteri with adenocarcinoma and in uteri with squamous cell carcinoma of the cervix before and after irradiation therapy. No culture was sterile in the "spontaneous" group with pyometra.

Sixteen of these, diagnosed as senile vaginitis, kraurosis, or leucoplakia, were treated with estrogen salve locally.

Although the series is too small for definite conclusions, there is a suggestion that estrogen therapy is more successful in the treatment of kraurosis than of leucoplakia.

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### THE USE OF METHYL TESTOSTERONE FOR THE RELIEF OF BREAST ENGORGEMENT IN THE PUERPERIUM

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IN THE past few years a number of reports have been published on the use of testosterone for the relief of breast engorgement in the puerperium<sup>1</sup> and on the inhibition of lactation.<sup>2, 3</sup> In these studies, the testosterone was administered parenterally, and the results were almost uniformly satisfactory. More recently methyl testosterone has been produced for oral administration. Realizing that the oral administration of hormonal substances is frequently ineffective, it was decided to carry out this study in order to ascertain its value, because many patients dislike injections. Except in cases of emergency an effective oral medication is to be preferred to a parenteral one.

This series consists of 50 cases. At no time during the treatment was there permitted a restriction of fluids, a reduction in diet, ice bags, saline cathartics, or any analgesics which might in any way interfere with the true evaluation of the efficacy of this medication. The cases were taken at random, some because of stillbirth, others because of unsatisfactory condition of the nipples, and still others because the mother preferred not to nurse.

In all cases, the medication was not started until the breasts were quite full, usually on the third or fourth day postpartum. This was done because it has been shown that testosterone is most effective at that time.<sup>4</sup>

During the first few days after delivery, there is still a sufficient amount of estrogen in the circulation to inhibit the pituitary from liberating its prolactin, and any testosterone given too early would be excreted without any lasting inhibitory effect. When the breasts begin

Until recently only aerobic cultures were routinely done as in most hospitals and therefore many cultures from pyometra were reported negative. However, our material showed positive cultures in 8 cases and no growth in 4 while no cultures were taken in 10 cases, none of these latter being recent. Four out of the 8 positive cultures and 2 out of the 4 negative cultures were anaerobic growths. It would seem therefore that cultures should always be grown both under aerobic and anaerobic conditions, for otherwise too many negative cultures will be reported.

With reference to sterile pyometra in carcinoma of the cervix, one-half of our 6 patients who had had previous radiation were sterile, and of 2 cases of carcinoma of fundus after previous operation or radiation, one patient was sterile and one was not cultured. I mention this because we had the idea, and I think most men have, that pyometra in the presence of cancer is always infectious.

In conclusion, I would like to emphasize the fact that in any study of the bacteriology of pyometra, all cultures must be grown under both aerobic and anaerobic conditions, otherwise results will be obtained that are not reliable. This is also most important when considering treatment.

DR. JOHN A. McGLINN, PHILADELPHIA, PA.—In order to have pyometra we must have three things: discharge, failure of drainage of the uterus, and infection. We find most of these cases among the malignant group, and next in order those among the senile group where we have obstructive lesions around the cervix and vagina. Formerly we saw quite a few of these cases due in part to faulty surgery. I can recall such cases following trachelorrhaphy, where we would fail to preserve the cervical canal for drainage.

I once made the statement that many of these cases were due to indiscriminate and faulty cauterization of the cervix, and have been taken to task for saying this. I have, however, a case of endocervicitis of my own treated by cautery that developed a hematometra and subsequently a pyometra. I attempted to maintain the patency of the cervix but failed and another surgeon eventually removed the uterus. I have also removed the uterus of another patient who had been cauterized by another physician with resultant pyometra.

Irradiation also plays a part in developing a stenosis. I do not think it occurs very frequently, because there is usually one factor missing, namely the discharge, but stenosis does occur. This brings up the point that we should be a little more careful in irradiating these so-called benign bleedings. In benign bleeding before the menopause I have long discarded the use of radium, and I have not had enough faith in hormones to control menopausal symptoms. In those cases which are postmenopausal, it is only anticipating what Dr. Scheffey may say in the next paper, to state that radium does not give protection against the later development of cancer. It has been my practice for some time in dealing with a woman who is past the menopause to remove the uterus entirely by the vagina.

DR. ARTHUR H. CURTIS, CHICAGO, ILL.—Gynecologists may be aware that there are two longitudinal ridges within the cervix but I have never heard them mentioned by any clinician or pathologist. The two ridges, usually located asymmetrically, anteriorly and posteriorly, tend to extend the entire length of the canal and, quite similar to the turbinates of the nose, are subject to very marked hypertrophy. Cysts so frequently encountered in the region of the internal os usually develop in the upper end of a hypertrophic longitudinal ridge. These ridges are important factors in the development of primary cervical obstruction and obstruction complicating endocervical therapy. It is, therefore, quite evident that these longitudinal ridges play a significant part in the etiology of pyometra.

DR. RAYMOND E. WATKINS, PORTLAND, OREGON.—Inasmuch as pyometra is so frequently associated with carcinoma of the uterus, it becomes a complication

which gives us a great deal of concern in the treatment of cancer. In reviewing our cases I have found that we had 17 patients with pyometra in the last eleven years. Eight of these were associated with carcinoma.

I recently visited a clinic in New York, and found that they ordinarily disregard pyometra, proceed with the placing of radium in the endometrial cavity, and only remove it in case the patient has a very high temperature reaction. We tried this plan, but there have been one or two severe reactions. While Dr. Carter has not discussed the treatment in any way, I would like to hear an expression from him regarding the management of pyometra, particularly previous to irradiation.

DR. CARTER (closing).—The practical nature of our findings will help to answer Dr. Watkins' question. We feel that pyometra should be suspected in the patients with squamous cell carcinoma of the cervix and in patients with adenocarcinoma of the corpus. We feel that it is safe following drainage to start x-ray therapy, but we should be most hesitant to insert radium into the cervical canal or into the corpus in the presence of infection without proper drainage for an appreciable time.

In our 39 patients with pyometra, anaerobic organisms were found in 22. In 8 other cultures, anaerobic organisms were found in symbiosis with aerobic organisms. Purely aerobic organisms were found in 9 cultures and in 8 other cultures were found in symbiosis with anaerobic organisms. We believe that the administration of x-ray therapy can be instituted safely provided the usual principles of maintenance of drainage and careful bacteriologic and clinical checking of the patient are followed.

The same problem arises in the patients with spontaneous pyometra. From our material it is seen that no culture was *sterile* in spontaneous pyometra. Following the drainage of spontaneous pyometra, we feel that curettement should be delayed over a period of weeks. We also feel that bacteriologic following is most important in determining when the curettement for diagnostic purposes should be done.

Bacteriologic checking of the patients is easily done by smear and culture methods by independent laboratory workers. This checking stresses the close correlation between the initial and subsequent bacteriologic findings.

The anaerobic organisms are poorly understood. They are difficult organisms with which to work. We feel that the term, "anaerobic streptococci," for the group as a whole is a poor term. Morphologically many strains resemble staphylococci. Separation and propagation of individual strains are difficult and, at times, impossible procedures.

Judgment as to the time to use the curette, radium, or x-ray following the evacuation of pyometra is difficult. Bacteriologic findings should help in answering some of the problems.

# THE EXPERIMENTAL PRODUCTION OF TOXEMIA OF PREGNANCY\*

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THE present experiments represent an attempt to demonstrate under conditions of laboratory control, the production in rabbits of the anatomic lesions which characterize uteroplacental apoplexy in women. Uteroplacental apoplexy, in the words of Couvelaire (1911) who named it, is characterized by "a colossal infiltration of blood in the uterine wall, occurring in the region of attachment of the membranes as well as in the region of placental attachment, cleaving the muscle bundles and dissociating certain bundles fiber from fiber. The ovaries are riddled with points of hemorrhagic effusion. The broad ligaments are infiltrated with blood. It amounts indeed to a veritable 'apoplexie utero-placentaire.' " The present experiments therefore involve the production of hemorrhage into the wall of the uterus and placenta which results frequently in premature separation of the placenta.

Since injury of this type occurs in women under conditions of obscure etiology, the present problem is: first, to determine whether or not identical anatomic lesions occur in a laboratory animal, and second, to evaluate the various factors introduced under controlled experimental conditions which cause normal pregnancy to terminate in uteroplacental apoplexy.

## METHOD AND MATERIAL

The present series includes 34 rabbits in which the course of pregnancy was experimentally altered by the injection of an extract of the urine of pregnancy, antuitrin-S (Parke, Davis and Co.), usually at twenty-five days which is the beginning of the last quarter of gestation. By this means ovulation was induced about the twenty-fifth day of pregnancy, so that at the normal end of gestation at thirty-two days there was present in the ovaries a fresh set of corpora lutea which had reached the stage of maximal size and function. The application of this method to the analysis of the factors concerned in parturition has been tested in previous investigations and the general nature of the anatomic abnormalities which were encountered in the uterus and placenta have been described (Snyder, 1934, Snyder and Deitrick, 1935, Snyder, 1938, 1939, Snyder and Koteen, 1939).

## OBSERVATIONS

*Macroscopic Appearance.*—In the present series of animals, the uterus was the site of gross anatomic changes. In a typical instance, dark

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purple areas of discoloration completely encircled the uterus at certain regions and extended far into the broad ligament (Fig. 2). The margins of the dark patches were irregular in outline and less deeply col-

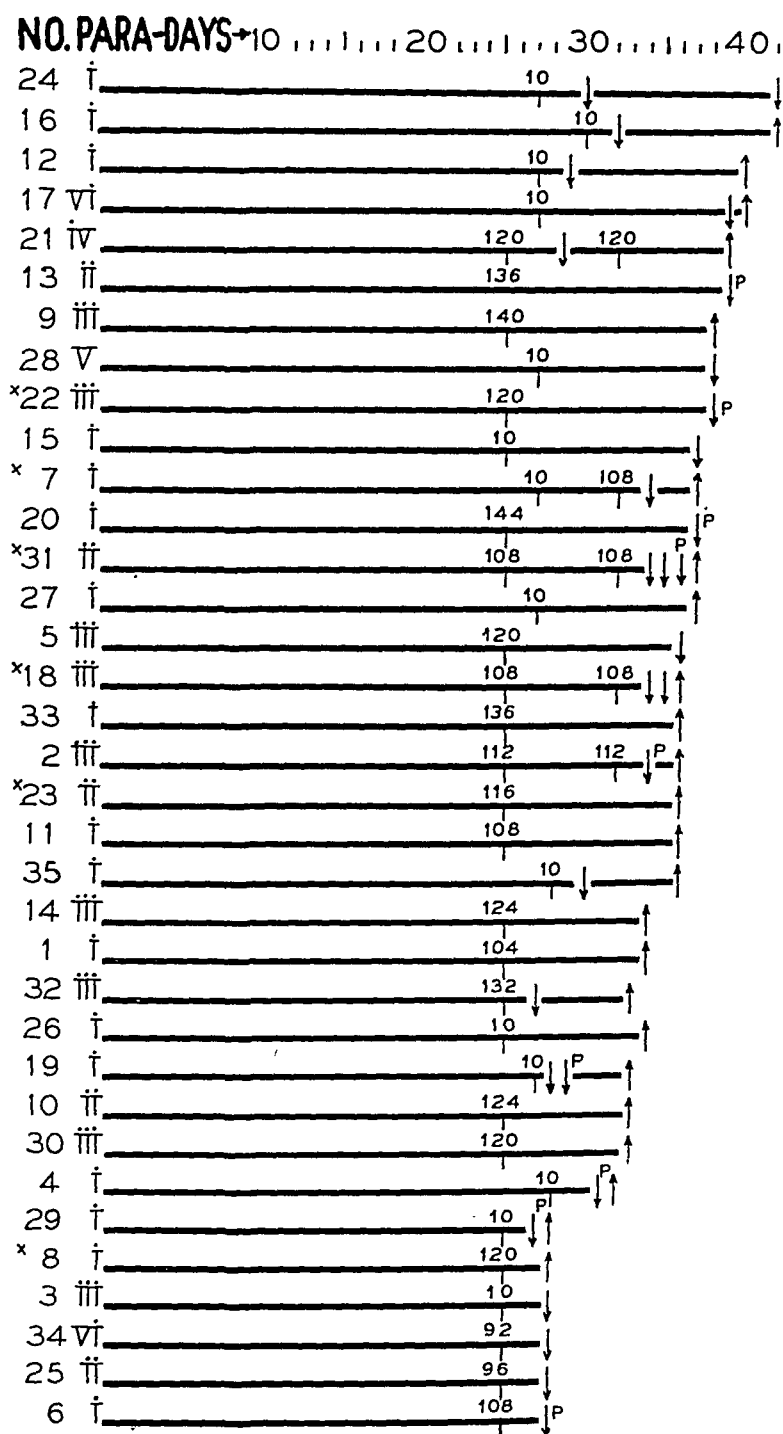


Fig. 1.—The course of pregnancy is charted in a series of 35 rabbits which showed hemorrhagic lesions of the uterus, such as characterize uteroplacental apoplexy in women. Each case is summarized, giving the time of injection of urine extract (antuitrin-S), the total dosage in rat units, and time of delivery. Complete emptying of the uterus is indicated by downward arrow with P; extrusion of part of a litter by downward arrow; delivery by hysterotomy by upward arrow. Maternal death during the experiment is shown by X. Of a total of 108 fetuses expelled before 36 days, 75 of them were born alive.

ored. Close inspection of the muscle layer of the wall showed strands which were distinguished by their pale color in contrast to the dark background caused by hemorrhage. There was actual separation of bundles of fibers by the dark-colored hemorrhagic extravasations which were wedged between them. Localized pressure with a finger tip failed to cause blanching, thus revealing that there was infiltration of the



Fig. 2.—Uteroplacental apoplexy. Animal 14 sacrificed ante partum at first sign of external vaginal bleeding; 34 days, 6 living fetuses.



Fig. 3.—Infiltration of blood into the uterine wall involving the region of placental attachment. Animal 29, sacrificed following the birth of 10 living fetuses at 27 days.

uterine wall rather than a mere engorgement with blood retained within the vessels. In the region of the implantation site, the hemorrhagic extravasation was especially dense and frequently extended into the adjacent broad ligament (Fig. 3).

Incision of the uterus in the region of discoloration showed that all three layers of the uterine wall were involved in the hemorrhagic



extravasation. In certain areas the hemorrhage into the tissues was so dense that the boundaries between layers were obscured, and the wall appeared homogeneous. Blood was frequently encountered within the uterus, having escaped to the region between the fetal membranes and the mucosa. The extramembranal hemorrhage could be seen directly through the thin uterine wall in many instances. Displacement of the blood promptly followed both the application and release of localized pressure upon the uterus, which thus aided differentiation from intramural bleeding. On opening the amniotic sac, blood-stained fluid was noted at times, but less frequently than extramembranal hemorrhage. In the lungs of fetuses which had died before delivery by hysterotomy, blood was readily demonstrated, and widely distributed throughout the alveoli (Snyder, 1940).

On cutting through the placenta, areas of hemorrhagic infiltration of the tissues were found. The maternal part of the organ was conspicuously involved. In the retroplacental region, the extravasation of blood could be linked with partial separation of the placenta from



Fig. 4.—Hemorrhagic infiltration of the placenta. Animal 11, sacrificed ante partum; 30 days, 4 postmature fetuses.

the uterine wall (Fig. 4). The escape of blood in the retroplacental area extended beyond the placental margin, and was continuous with the hemorrhage separating the fetal membranes from the decidua vera (Fig. 5).

Incision of the broad ligament showed especially dense infiltration of blood in the loose connective tissue between the folds of the mesometrium.

Upon first opening the peritoneal cavity, an increase in the normal amount of peritoneal fluid was encountered, which was markedly stained with blood at times. The serosal region of the uterine wall was involved extensively and infiltration of blood was seen at many areas where the dark discoloration of intramuscular hemorrhage was not evident. A deep longitudinal fissure marked the site of rupture of the uterus in one animal in which a full-term fetus escaped into the peritoneal cavity.

*Microscopic Examination.*—In the animals of the present series the extravasation of blood into the decidual, muscular, and serosal regions

of the uterine wall has been verified by microscopic examination. Correlation of the histologic findings with the functional changes of the uterus may be illustrated by specific cases.



Fig. 5.—Partial separation of the placenta; retroplacental hematoma and escape of blood between the membranes and uterine mucosa. Animal 7, died at 37 days; 6 postmature fetuses in the uterus, 2 others having been expelled at 34 days.

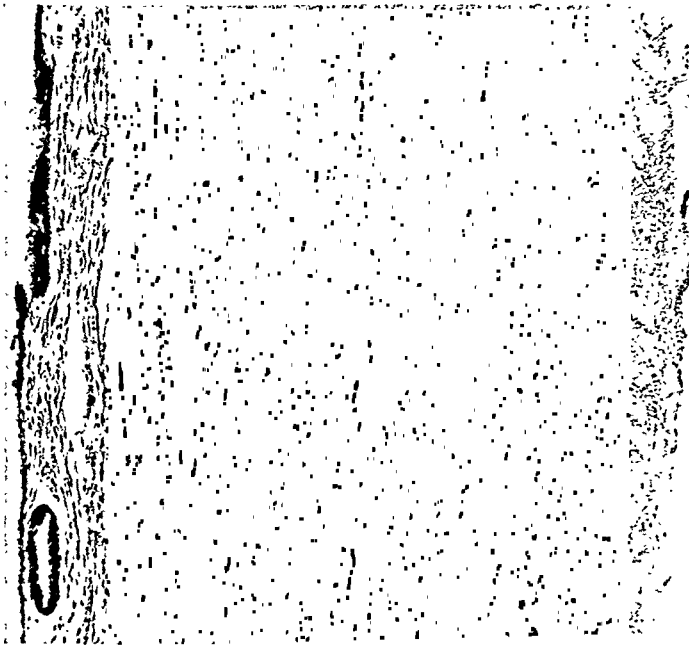


Fig. 6.—Wall of uterus showing hemorrhagic infiltration (Animal 14).

In an animal (No. 14) which was sacrificed at the first appearance of external vaginal bleeding at thirty-four days, and before the birth of any fetuses, the uterus contained six postmature fetuses which showed active movements. A transverse section taken through the entire uterus

and placenta, when stained with eosin and hematoxylin presented a brilliant picture even to the unaided eye, illustrating the extensive hemorrhage into the tissues (Fig. 2). The lateral wall showed dense infiltration of the serosal and muscular regions (Fig. 6). Separation of bundles of muscle fibers by huge extravasations of blood was striking

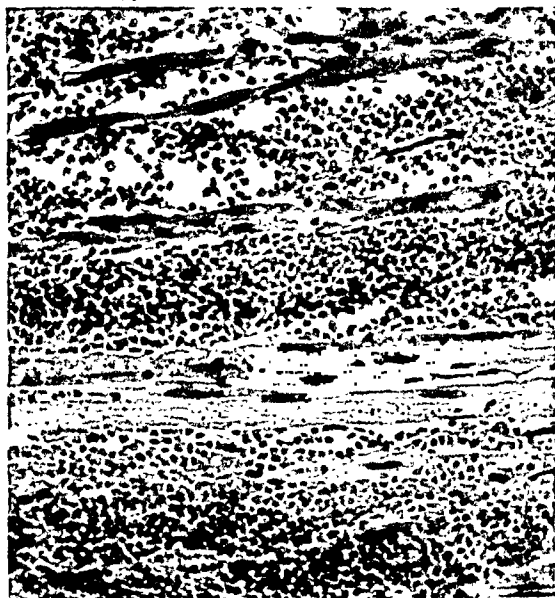


Fig. 7.—Separation of muscle fiber bundles (Animal 14).



Fig. 8.—Broad ligament infiltration (Animal 14).

ing and was characteristic of the state of a large part of the uterine wall (Fig. 7). In connection with the escape of blood in the serosal layer, there was found in this animal a blood-tinged peritoneal fluid of excessive amount. The decidua vera was less extensively infiltrated than the other layers.

A section of the broad ligament revealed dense infiltration between folds of the mesometrium and in the serosal region (Fig. 8).



Fig. 9.—Retroplacental hemorrhagic infiltration (Animal 14).

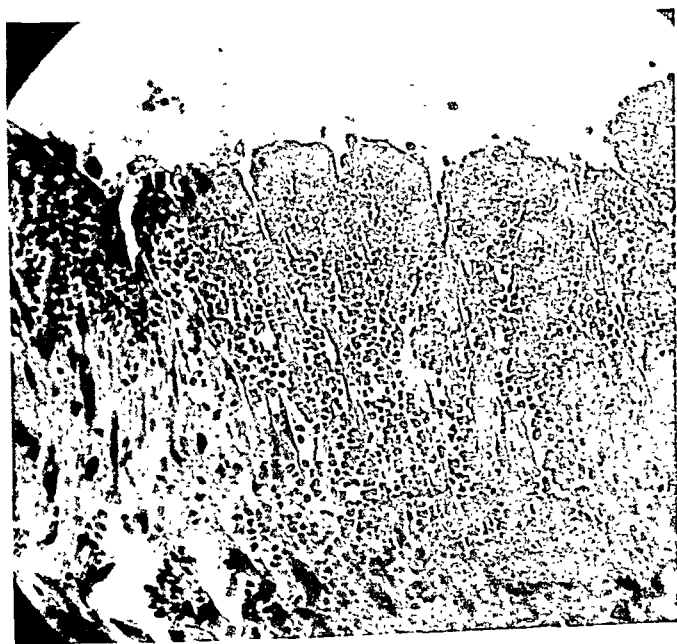


Fig. 10.—Perivascular infiltration. Animal 5, sacrificed at 36 days; 4 postmature fetuses expelled, 5 remaining in the uterus.

The site of the attachment of the placenta showed marked infiltration of red blood cells which was limited to the zone of connective tissue interposed between the maternal placenta and the muscle layer of the uterus (Fig. 9). Sections of the maternal placenta of this animal (No. 14) did not show hemorrhagic infiltration. The escape of blood

was evident, extending from the margin of the placenta laterally between the surface of the decidua vera and the membranes which were reflected by it.

Hemorrhagic infiltration of the maternal portion of the placenta was illustrated in an animal (No. 11) sacrificed at thirty-six days. None of the litter had been born and no external vaginal bleeding was noted. The four fetuses which occupied a single horn of the uterus were dead but not macerated, and their stage of development was the maximal attained during intrauterine life. Extravasation of blood extended from the muscular layer of the uterus through the entire thickness of the maternal portion of the placenta (Fig. 4). Partial separation of the placenta associated with a striking retroplacental hematoma was clearly shown in Animal 11. The animal (Fig. 5) was found dead on the thirty-seventh day. Two stillborn postmature fetuses had been expelled and 6 additional fetuses of excessive size remained in the uterus.



Fig. 11.—Perivascular and myometrial infiltration (Animal 5).

Hemorrhagic infiltration of the implantation region was evident in Animal 29 which was sacrificed at twenty-eight days (Fig. 3). The entire litter of immature fetuses was expelled alive at twenty-seven days. Microscopic examination revealed dense extravasations, especially involving the decidual layer in the region of the placental attachment. Various stages in the partial dislodgment of the placenta associated with decidual extravasations may be found by sacrifice of animals before completion of labor.

Blood vessels were also the site of infiltrations of red blood cells in the perivascular area (Fig. 10). In Animal 5, sacrificed at thirty-six days, 4 large, postmature fetuses had been stillborn and 4 additional fetuses remained unexpelled. A dense extravasation of blood occupied the perivascular sheath and at certain areas extended into the myometrium (Fig. 11).

To summarize briefly, the anatomic lesions in the uterus were characterized by hemorrhage into the uterine wall, involving all three layers. Throughout the entire decidual lining of the uterus, extravasa-

to fill, it is indicative of the fact that the supply of estrogen is so greatly diminished that it no longer prevents the pituitary from liberating its prolactin. Just how the testosterone does its work in inhibiting lactation has not as yet been proved. It might inhibit the pituitary from liberating the prolactin, or it might antagonize the lactogenic hormone itself, or it might depress the receptivity of the breast so that it cannot be stimulated by the prolactin.

Hamilton<sup>5</sup> has shown an inhibiting effect on the hypophysis as well as histologic changes from testosterone, but Reece and Mixner<sup>6</sup> employed testosterone propionate in sexually matured spayed rats, and they found that the yield of pituitary lactogen was augmented. Hence the *modus operandi* is still debatable.

In presenting Table I, the column designated "breast before treatment" is given in numbers. The number "4" represents a breast which is full, firm, tender, painful, and caked. Number "3" is a breast which has the above qualities to a lesser degree. When a breast is full but only slightly painful or tender, it was represented by the number "2."

#### DISCUSSION

The results were classified as good if the patient acquired almost complete subjective and objective relief. That is, the breasts became neither painful nor tender to touch. A small percentage of these continued to lactate to a minor degree for several days after the treatment was discontinued. But our purpose of the treatment was not to prevent lactation, but rather to cure the pain and discomfort of weaning.

Those patients who had moderate relief of pain and tenderness were designated as fair. Those patients who showed no appreciable relief were designated as poor.

There were 44, or 88 per cent, with good results, 4, or 8 per cent, fair, and 2, or 4 per cent, who had poor results.

Of the cases designated as good, there were two which require additional information. One, J. W., was a woman whose breasts were engorged and painful. She was nursing her infant. In this case, 60 mg. were given, divided into three doses. This relieved the pain and tenderness, and permitted her to nurse satisfactorily. The infant continued to gain well with the subsequent milk. The second case (F. B.,<sup>1</sup>) was a woman who developed an acute exacerbation of a chronic cholecystitis. She was given daily small doses of magnesium sulfate, and was on a restricted gall bladder diet. Therefore, it is difficult to state whether the improvement in her breasts was due to the methyl testosterone or to the diet restriction and magnesium sulfate, or to a little of both.

There were two patients who exhibited moderate hirsutism. The results were fair in one and poor in the other. Both these women had android pelvises. The voice was not deep although it was a little husky in one of them. It is possible that in those women with androgenic tendencies a much larger dose would be required to create a small effect due to the piling up of this substance in the system.

of necrosis (Fig. 12). In Animal 5, which was sacrificed at thirty-six days during labor, as previously described, there was widespread damage of the kidneys (Fig. 13). The death of 6 animals of the total of 34 rabbits in the course of experimentally altered pregnancy was direct evidence of the magnitude of the functional injuries.

#### RELATION OF PHYSIOLOGIC TO ANATOMIC CHANGES

The physiologic changes are no less striking than the anatomic alterations which accompany induction of ovulation. Functional disorganization of labor as shown by either inhibition of parturition or by the premature expulsion of fetuses is linked with structural injury which may involve the entire uterine wall. A notable feature, however, is the birth of living offspring despite these conspicuous abnormalities. Thus, an indication is given of the narrow margin which separates the physiologic from the pathologic consequences of pregnancy.

In the present series of animals, a single injection of an extract of urine of pregnancy, antuitrin-S (Parke, Davis and Co.), about the beginning of the last quarter of gestation, resulted in the induction of ovulation. In the presence of a fresh set of corpora lutea in the ovaries, normal parturition at term failed to occur. The time of onset of parturition may be either postponed or hastened, the reaction being determined by the dosage and by the stage of pregnancy at injection. These factors may be adjusted so that in a given animal both types of response can be elicited; certain fetuses in a litter may be cast out prematurely and alive, while the rest of the litter survives in the uterus and eventually attains postmature stages of development.

In connection with the control of the duration of gestation in the rabbit by the induction of ovulation, it is especially noteworthy that the change in the time of onset of parturition, whether postponing the termination of pregnancy or hastening it, still followed a definite pattern. Emptying of the uterus occurred either at the beginning of the sixteen-day life span of the induced corpora lutea or at the end of it. Since living fetuses were born when pregnancy was interrupted by this method, the procedure offers the functional equivalent of spontaneous parturition. The normal mechanism of labor seems to be in operation except at an earlier or later time than is usual. The duration of pregnancy may be formulated in terms of hormonal function.

The striking physiologic alteration of the course of pregnancy prompted investigation of the anatomic basis of parturition under these conditions. Examination of the uterus in animals in which parturition set in on the second or third day following injection revealed striking changes in the decidua. The escape of blood from the vessels and infiltration of the area of attachment of the placenta was associated with the accumulation of blood between the membranes and the surface of the decidua vera. At the margin of the placenta, hemorrhage was conspicuous. Dense retroplacental extravasation of blood resulted in partial separation of the placenta from its site of attachment. The origin

tions were found, both in the stroma of the retroplacental region as well as outside of this area, i.e., in the decidua vera. The maternal portion of the placenta is frequently a site of extravasation of blood which may result in partial separation of the placenta from the uterus. In the muscle layer the escape of blood into the tissue was linked with the separation of bundles of fibers over the entire circumference of the wall in certain regions. In the serosa, outpouring of blood is likewise extensive.

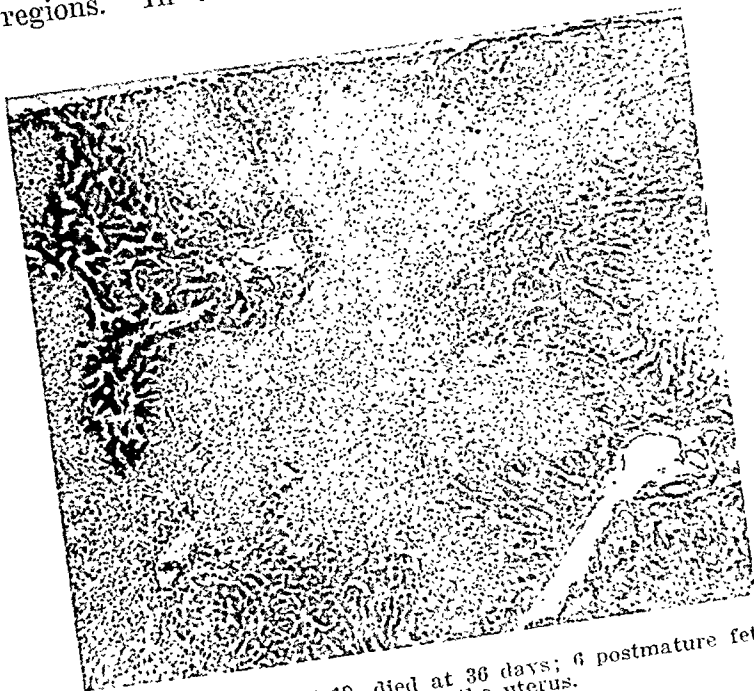


Fig. 12.—Liver necrosis. Animal 18, died at 36 days; 6 postmature fetuses expelled, 1 remaining in the uterus.

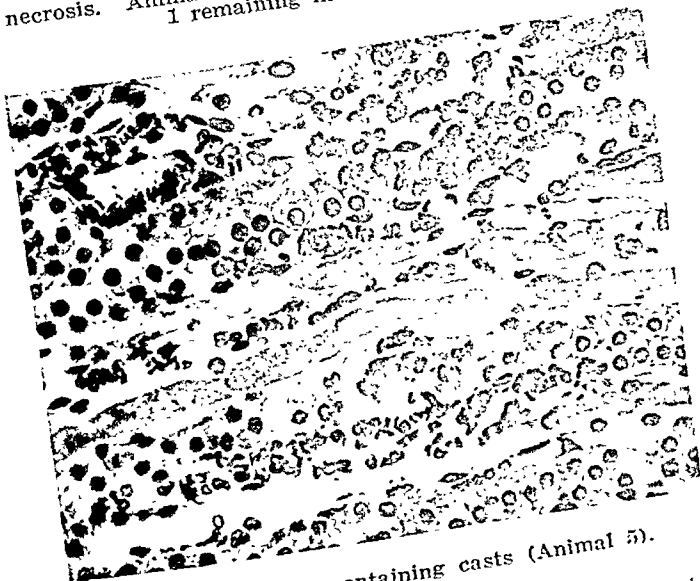


Fig. 13.—Kidney containing casts (Animal 5).

Histologic examination of other organs obtained at autopsy revealed clearly that injuries involved other tissues besides the generative tract. Striking changes were found in the liver, kidneys, lungs, and other organs. For example, in Animal 18 which died at thirty-six days following birth of 5 postmature fetuses, the liver showed extensive areas



term was prolonged a week past term. (3) Microscopic examination of the ovaries and uterine mucosa of the nonpregnant horn in unilateral pregnancy; there were changes characteristic of active corpora lutea.

The survival of the fetuses within the uterus following inhibition of parturition and their attainment of extreme stages of postmature development afforded additional evidence of the functional state of the decidua and placenta. Furthermore, after the limit of intrauterine survival was reached at thirty-five days, the dead fetuses were not cast out at once but usually were retained within the uterus until about the forty-first day or the end of the life span of the induced set of corpora lutea. Thus, the outstanding physiologic change in the uterus at term and during postmaturity involved the musculature rather than the decidua. It was during this period likewise that the uterine musculature was involved conspicuously not only in functional change but also in striking anatomic lesions, namely, extensive hemorrhagic extravasations.

The time sequence in which the hemorrhagic extravasations appear as well as the difference in the site of bleeding in the layers of the uterine wall afford clues which aid in the attempt to trace the nature of the injury which marks the transition from the normal uterus to that of uteroplacental apoplexy. Under the conditions of the present experiments, the process of labor may be slowed down so that the duration of the period from the onset of expulsion of the first fetus until the extrusion of the last one of the litter is two weeks. The dissociation of the mechanism of labor followed a regular pattern and occurred in two phases. One period of the expulsion of fetuses was on the second and third days following ovulation; the second period of expulsion was about two weeks after ovulation. The two phases differed strikingly with regard to the changes which occurred in the uterine wall, although both led to the emptying of the uterus. In the first period, decidual changes predominated, and the muscular contractility was minimal; in the second phase muscular contractions were uninhibited, response to pituitrin had returned, and decidual changes were slight. In both periods of expulsion of fetuses, anatomic changes of the uterine wall readily passed beyond normal limits to the pathologic state characterized by extravasations of blood. Uteroplacental apoplexy involving premature separation of the placenta was thus associated with the mechanism of labor. Exaggeration of the normal mechanism to a pathologic state was illustrated in so far as the hemorrhagic lesions were not entirely irregular but occurred in a definite anatomic and chronologic pattern. In emptying of the uterus, two cardinal factors stand out, namely, the decidual and the muscular; evidence of their respective roles in parturition is obtained by attempting to exhibit them one at a time, since normally they are not dissociated.

In brief, starting with normal pregnancy, the anatomic and physiologic changes which characterize premature separation of the placenta

was revealed of the vaginal hemorrhage of fresh blood which preceded the expulsion of living fetuses by hours in some cases. Similarly there was evidence of the structural changes associated with excessive postpartum hemorrhage which frequently occurred.

Since the birth of living fetuses occurred in the course of induced labor by this method, there remains to be considered in addition to the decidual changes, a second factor, namely, the state of contractility of the uterine muscle. In this connection it was noted upon examination of the uterus that while certain placental areas were the sites of hemorrhagic extravasations which result in dislodgment of the product of conception, the rest of the implantation areas of a litter were not involved. The fetuses remaining in the uterus continued to grow to extreme stages of postmature development, being finally cast out at the end of the life span of the induced corpora lutea. The fact of the survival of the fetuses which were implanted adjacent to those which were cast out alive was direct evidence of the relatively quiescent state of the uterine muscle, although still functioning adequately for the expulsion of living offspring. Dislodgment of certain fetuses of a litter was not caused by muscle contraction alone but was related to structural changes of the decidua, involving the placenta. Induction of parturition was effected by means of induced premature separation of the placenta rather than by a muscle response.

At this point one may pause to recall a general principle with regard to the relation of the ovary to the uterus in all mammals, namely, that the development of a fresh set of corpora lutea is invariably linked with structural changes of the uterus involving hyperemia and growth (Swezy, 1935). Since ovulation can be induced experimentally in the rabbit during pregnancy at any time which is desired (Snyder and Wislocki, 1931), it is evident that the pregnant uterus may be subjected to increase in the stimulus which normally results in hyperemia, the magnitude of the increase being of such amount as is afforded by the addition of a fresh set of corpora lutea in the ovaries.

The question also arises as to what state of functional activity of the uterine muscle was associated with the intramuscular extravasation of blood. Hemorrhagic infiltration of the muscular layer was a striking feature of the uterus in which full-term or postmature development had been reached under the present experimental conditions. Functionally, there was failure of the uterus to expel its contents at term; uterine inertia was marked. Examination of the ovaries revealed a fresh set of corpora lutea at the stage of full development. Evidence that the induced set of corpora lutea were functional was afforded not only by the quiescent state of the uterine muscle but also by other findings (Snyder, 1934): (1) Absence of pituitrin effect; pituitrin administered at term failed to induce parturition despite a dosage 1000 times greater than the amount normally effective. (2) Absence of ovulation after coitus; the period of inhibition of ovulation which normally ended at

The cycle is under hormonal control. Experimental introduction of ovulation during pregnancy is a method for changing the hormonal coordination at various stages of pregnancy as desired, while keeping constant the endocrine pattern of the ovulation cycle. Experiment by this method may reveal whether or not the endocrine balance can be altered sufficiently to produce a modified pattern of pregnancy such as lengthening it or shortening it, or slowing certain phases such as parturition, while still preserving a physiologic outline. Increase in stimuli may be traced in terms of increased responses until finally the break in adjustment appears without loss of all physiologic relations. The sites of injury may be traced to exaggeration of the physiologic processes. Furthermore, the period of pregnancy at which the stimulus is introduced may be varied. Alteration of the hormonal or chemical coordination of pregnancy may thus result in abnormalities which vary according to the period of pregnancy and the intensity of the stimulus.

The systemic effects and involvement of visceral organs are ultimately connected with known experimental procedures, since in the beginning pregnancy was normal. Thus, there is evidence of the type of injury and the nature of the toxic process.

It is known that in many respects the embryo has a special physiology. To a considerable degree the maternal organism as well during normal pregnancy shows greatly altered reactions, especially in magnitude. The magnitude of the physiologic changes which characterize pregnancy in contrast to the nonpregnant state may be illustrated by the two extremes of response which are observed following injection of a drop of urine extract (antuitrin-S). In the immature rabbit there is little or no effect. In the pregnant animal injury may attain the proportions of general systemic involvement or intoxication resulting in death.

#### CONCLUSIONS

1. Uteroplacental apoplexy involving premature separation of the placenta was observed in rabbits following induction of ovulation by injection of urine extract (antuitrin-S) during pregnancy.

2. Anatomic evidence showed that injury attained the magnitude of general systemic changes or intoxication, resulting in death.

3. Physiologically, the genesis of the injury or nature of the toxic process was traced ultimately to alteration of the hormonal coordination of pregnancy.

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and uteroplacental apoplexy have been traced in relation to the labor mechanism; and in turn the pathologic processes have been linked with the endocrine regulation of gestation, especially the factors concerned in the duration of pregnancy.

#### RELATION TO CHANGES IN THE REST OF THE BODY

In women uteroplacental apoplexy has long been linked with far-reaching changes throughout the body. Upon the basis of clinical findings and the evidence obtained at autopsy, it has been regarded as a manifestation of toxemia of pregnancy. "Accidental hemorrhage is an intoxication of the same kind which causes albuminuria, eclampsia, or eclampsia" (Essen-Möller, 1913). "In accord with this view are found practically all who have studied the subject, among whom may be mentioned: Bar, Couvelaire, Williams, Smyly and Ley" (Willson, 1922). Fitzgibbon (1918) proposed the term "antepartum toxemic hemorrhage" for the disease. As the uterine lesion of the eclamptic type of toxemia, the significance of uteroplacental apoplexy was comparable to such striking changes as hemorrhagic hepatitis, extensive necrosis in the kidney, or hemorrhage into the brain. Schmorl's findings at autopsy were emphasized; namely, that eclampsia involved a more far-reaching disorder than could be defined by restricting it to symptom-like convulsions which often were not observed, as he noted, although the liver, kidneys, brain, and other organs might show well-marked lesions in women dying at the time of labor.

How to approach the reconstruction of toxemia in a laboratory animal has long been puzzling. The embryologic method involves tracing of the complex back to the rudimentary by taking earlier and earlier stages in the development of a structure or function. The problem is to reconstruct experimentally disorders of pregnancy which involve both function and structure, early as well as late pregnancy, occurrence in not totally irregular fashion and changes in the organism as a whole as well as in specific tissues.

The question is, what features of toxemia should one select for experimental analysis: convulsions, hypertension, albuminuria, edema, liver necrosis, kidney damage, or uteroplacental injury? Since all may be manifest in the same individual in the course of toxemia of pregnancy, a choice of any one appears to be rather arbitrary. If one turns from pathologic pregnancy to consider the factors chiefly concerned in the maintenance of the delicate physiologic balance of normal pregnancy, it is apparent that the mechanism of the sexual cycle is intimately involved. There is evidence that pregnancy is composed physiologically of a series of cycles which are not completely suppressed, the cycles being the functional units or links in the chain of events constituting pregnancy by which a timing mechanism is set at a given rate for a species (Snyder, 1938).

briefly to present some of these findings indicating that a similar condition develops in a different species.

Anterior pituitary extracts often prolong gestation in the rat. This is at times accompanied by separation of the placenta and death of the fetus in utero, prolongation of parturition, and failure of the birth mechanism. Unfortunately, we did not realize at that time the possible connections of these findings with the toxemias of pregnancy, and other organs were not studied.

Six rats delivered at twenty-three to twenty-six days instead of twenty-two days. These rats received growth hormone beginning from the sixth to the tenth day of pregnancy and continued to delivery. Thirty-eight of the 42 young were stillborn, macerated, or being resorbed. Vaginal bleeding preceded delivery and labor was often prolonged over several days. The normal birth mechanism seemed to fail completely.

One rat injected from the twelfth day on died on the twenty-sixth day. The uterus was found filled with blood with the placentas detached and surrounded by large clots of blood. The young were black and partially resorbed.

Six rats were injected beginning with the tenth day and autopsied from the twenty-fourth to the twenty-seventh day of pregnancy. On the twenty-fourth day the young were still alive if the placentas were attached. The placentas were usually partially or entirely detached, however, and the young were then dead, often for a long period of time, and were black and being resorbed. Sometimes the placentas adhered to the uterine wall but were easily detached so that two or more placentas could be removed at one time.

Cesarean section was performed on 2 rats on the twenty-fourth and twenty-six days of pregnancy. Both had received hormone from the tenth day. The rat on the twenty-fourth day had a grossly normal litter but the young were sluggish and there were clots around the placentas. The rat autopsied on the twenty-sixth day had partially delivered two dead fetuses previously but the rest of the litter of eight were dead and being resorbed.

Four rats were autopsied at term. These rats had received hormone from the twelfth day. The young were all normal and living with the exception of 3 of one litter which were not found and whose placentas were abnormal or reduced to "tarry" masses. The remaining placentas in this rat and two other rats were firmly attached, but some of the placentas of the fourth rat had large blood clots.

| EXTRACT NO.   | DELIVERY 22-23 DAY | DELIVERY LATER THAN 23 DAY | AUTOPSY 22 DAY | NO. PREG. | TOTAL RATS | TOTAL PREG. | TOTAL PROLONGED PREG. |
|---------------|--------------------|----------------------------|----------------|-----------|------------|-------------|-----------------------|
| Phyone 32     | 4                  | 11                         | 0              | 2         | 17         | 15          | 11 (73%)              |
| Misc.         | 11                 | 11                         | 3              | 1         | 26         | 22 + 3      | 11 (50%)              |
| Phyone 34     | 7                  | 1                          | 0              | 0         | 8          | 8           | 1 (12.5%)             |
| Special Ext.* | 18                 | 5                          | 0              | 0         | 23         | 23          | 5 (23%)               |
|               | 40                 | 28                         |                |           | 74         | 58 + 3      | 28 (48%)              |

\*Fractionations of these extracts show that the factor prolonging pregnancy is a contaminant of the growth hormone and is more soluble at pH-7 than is the growth hormone.

DR. SNYDER (closing).—With regard to the state of the fetus, the first specimen I took is a typical one. The fetus was alive and the animals were killed because of external bleeding. Of course, the study has been amplified a great deal. We have had animals that have retained their fetuses for several hundred days but that is not a part of this discussion.

This is certainly a complicated problem and I have tried to confine the description to anatomic terms based on the rabbit. Of course, the hormonal relationships in the rabbit are a problem in themselves.

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### DISCUSSION

DR. ROBERT A. ROSS, DURHAM, N. C.—Dr. Snyder has studied the effect of pregnancy urine extract on the pregnant and nonpregnant uterus of rabbits and has noted gross and histologic changes in the pregnant uterus similar to the human uterus with uteroplacental apoplexy. He properly believes that these observations might aid in answering the problem of this condition in the human being.

Naturally one realizes the danger of interpreting animal experimentation in terms of the human being, and, in this particular study, one recalls the work of Evans and others which shows the highest titers of the gonadotropes to be at the second and third months of gestation. Also in the human being we know that only 50 per cent of cases of abruptio placentae have a toxemic background. In a study of 34 women who died in the eclamptic state and on whom complete autopsies were obtained, we found basophilism of the pituitary in only one instance and in this individual also was found hyperluteinization of the ovary. If a profound derangement of the endocrine system is constantly present in toxemias and if there is uniform increase in the gonadatropes, one might expect more histologic evidence than we found in these 34 women. The essayist's work is however, consistent with the conclusions of Smith and Smith which had to do with changes in the gonadatropes and estrogen in the toxemias.

DR. GEORGE VAN S. SMITH, BROOKLINE, MASS.—Dr. Snyder has produced, experimentally, lesions similar to those of specific toxemia of human pregnancy. He has produced them by hormone deprivation.

The endometrium of the human being at the time of menstruation may be said to go through a process of apoplexy. The monumental work of Markee has led him to believe that the cause of the changes in the endometrium, before and at the time of menstruation, is a local factor resulting from hormone deprivation. In the menstrual discharge, we have found what appears to be a specific toxin which we believe explains the behavior of the endometrium following hormone deprivation.

We have found that urinary hormone changes similar to those before and at menstruation precede and accompany labor and also toxemia of late pregnancy, indicating that hormone deprivation is a prelude to these events. Our present belief is that any disturbance which brings about hormone deprivation in the last trimester of pregnancy results thereby in a metabolic change in the uteroplacental area with the formation of a substance to which may be attributed the final manifestations of toxemia.

DR. NICHOLSON J. EASTMAN, BALTIMORE, MD.—May I ask the essayist when the females were sacrificed? If the lesions described were present before the thirty-second day of pregnancy, they might quite conceivably be attributed to hormonal influences. If, on the other hand, they occurred in association with artificial prolongation of pregnancy in animals sacrificed, let us say, on the thirty-fifth or thirty-sixth day, one cannot help but think of overdistention of the uterus as an etiologic factor. It would seem important that this question be answered.

DR. FRED L. ADAIR, CHICAGO, ILL.—A number of years ago Dr. Ruth Watts and I undertook, in our Clinic, some investigations in regard to the effect of growth hormone upon gestation. We were more particularly concerned with the possible relationship between the administration of the growth hormone and the development of the fetus. In connection with this work on the rat, certain accidental findings were encountered which fit in with Dr. Snyder's thesis this morning. I would like

vagina a totally unreasonable risk is assumed. Reoperation for recurrent cystocele, intestinal obstruction, or enterocele are not rare following operation by competent surgeons.

With these limitations in mind, we may say that vaginal hysterectomy is a safe procedure well within the compass of the competent gynecologist for the conditions and indications outlined. Beyond this it becomes a hobby, whether expertly performed or inexpertly inflicted.

In the author's group of hysterectomies, there were 83 cases of vaginal hysterectomy. This does not include two which were attempted but thwarted by old abdominal fixation operations, and successfully completed abdominally. Two developed enteroceles which were subsequently corrected. There were 6 recurrences of cystocele. The bladder twice was inadvertently opened, but sutured in layers and the vaginal hysterectomy proceeded with. No fistulas resulted. There were no immediate operative deaths. One 68-year-old patient died six weeks postoperatively at home from some undetermined abdominal condition. Three patients showed evidence of intestinal obstruction. One was from fecal impaction due to improper preoperative preparation. Only one required operation. A loop of ileum was kinked and adherent in the culdesac and release of the obstructed bowel sufficed as a cure.

The trend toward total hysterectomy for all non-malignant uterine disease prompts an unbiased inquiry into the reasonability as well as the results of the methods commonly chosen.

The controversy of complete versus supravaginal hysterectomy would seem to indicate a move from a relatively simple operation to one immediately awesome and threatening in its application. For the majority of patients either operation may be done with safety and facility by any competent operator. What then are the further steps which one takes when the contemplated supravaginal operation is converted into a total hysterectomy? Briefly, these:

The bladder is separated not only from the cervix but also from the anterior vaginal vault, by dividing the uterovesical fascia. The uterine vessels are well exposed, ligated and divided about 1 cm. lateral to the internal os, and the stumps pushed out and away from the uterus, carrying the ureters out with the fascia and away from danger. The thickened endopelvic fascia lateral to the cervix, the ligament of Mackenrodt, is clamped, cut and sutured, thus freeing the cervix laterally. The uterosacral ligaments are tied and cut close to the internal os and the peritoneum divided between them. The vagina is opened anterior to the cervix, or a posterior vaginal opening may be chosen, and the vagina circumcised close to the cervix. The vaginal mucous membrane and fascia is then closed, the vagina supported by re-attaching the broad, round and uterosacral ligaments and the operative area reperitonized.

The sole advantage of a complete hysterectomy lies in the removal of the cervix. The operation combines therapy for existing cervical

## SELECTIVE HYSTERECTOMY FOR NONMALIGNANT UTERINE DISEASE\*

EDWARD G. WATERS, M.D., F.A.C.S., JERSEY CITY, N. J.

THE term "selective hysterectomy" implies that diverse operative procedures are available for adequately treating nonmalignant uterine disease. The qualifying adjective infers that limitation of hysterectomy to but one operative technique is unsound.

A diseased uterus may be removed by total vaginal hysterectomy, supravaginal hysterectomy, or total abdominal hysterectomy. The subject matter here presented is based upon relevant literature and personal experiences for the past fifteen years and represents an inquiry into the factors which determine choice of operation for the condition encountered.

With few exceptions as to operators and indications, vaginal hysterectomy is reserved for patients with moderate-sized tumors and large vaginal passages, or as an associated procedure accompanying correction of prolapse. Resorting to a Schuchardt incision to secure room for vaginal hysterectomy is rarely justified. It is a bloody, easily infected incision which heals poorly and with much granulation tissue. One must carefully assess the presumed value of a contemplated vaginal operation against the frequent perils of this incision. It has been my experience that if one excludes cases with procidentia or ample parous passages, abdominal hysterectomy is safer and accompanied by fewer complications. Since vaginal hysterectomy is performed largely on selected and pathologically uncomplicated cases, the admittedly lower mortality and morbidity rates are anticipated. It is seldom a shocking operation and the postoperative course is usually excellent. To avoid operative risk the patient must have a freely mobile uterus, and the cervix must descend with traction to the vulva. Even with palpably mobile structures, previous operations make the pelvic status uncertain until the operation is well advanced, and the vaginal route should be avoided unless the exact nature of such pelvic surgery is known. When a tumor requires morcellation to reduce it, unexpected dangers may arise. I know of two nephrectomies necessitated by vaginal removal of large tumors by morcellation.

With suitable local conditions and indications vaginal hysterectomy is the best operation for totally removing the uterus, especially in old or obese women or in poor surgical risks. When the vagina is small, the uterus fixed or adherent, and the uterine tumor large, the surgeon's grief may know no bounds should he attempt it, and through such a

\*Read, by invitation, at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.



TABLE I

| PT.    | AGE | PARA | GRAV. | CHAR. OF DELIVERY | DAY P.P. OF 1ST. DOSE | DOSE MG. | BREAST BEFORE TREATMENT | RESULTS | INVOLUTION    | COMMENT   |
|--------|-----|------|-------|-------------------|-----------------------|----------|-------------------------|---------|---------------|---|
| E. A.  | 29  | i    | i     | Spont.            | 6th                   | 270      | 4                       | Poor    | Normal        | Mod. hirsutism. Breast pumped until fifth day Improved with ergotrate |
| M. A.  | 25  | ii   | ii    | Spont.            | 3rd                   | 150      | 3                       | Good    | Subinvolution |   |
| A. A.  | 32  | i    | ii    | Spont.            | 3rd                   | 150      | 4                       | Good    | Normal        |   |
| E. A.  | 29  | iii  | iii   | Low forceps       | 3rd                   | 240      | 4                       | Good    | Normal        |   |
| R. B.  | 24  | i    | i     | Spont.            | 4th                   | 90       | 4                       | Good    | Normal        |   |
| F. B.  | 31  | ii   | ii    | Spont.            | 3rd                   | 60       | 4                       | Good    | Normal        | Gall bladder attack (see discussion, F. B. i)                         |
| E. B.  | 30  | ii   | ii    | Spont.            | 3rd                   | 150      | 4                       | Good    | Normal        |   |
| R. B.  | 20  | ii   | ii    | Spont.            | 4th                   | 150      | 3                       | Fair    | Normal        | Nursed baby third day   |
| E. B.  | 23  | i    | i     | Spont.            | 4th                   | 90       | 4                       | Good    | Normal        |   |
| D. B.  | 26  | ii   | ii    | Spont.            | 3rd                   | 240      | 3                       | Good    | Normal        |   |
| F. B.  | 34  | i    | i     | Low forceps       | 4th                   | 150      | 4                       | Good    | Normal        |   |
| F. C.  | 29  | i    | iii   | Spont.            | 4th                   | 150      | 4                       | Good    | Normal        |   |
| C. C.  | 24  | i    | i     | Spont.            | 3rd                   | 270      | 4                       | Good    | Normal        |   |
| C. C.  | 24  | i    | i     | Spont.            | 4th                   | 150      | 3                       | Good    | Normal        |   |
| C. C.  | 27  | ii   | ii    | Spont.            | 3rd                   | 210      | 3                       | Good    | Normal        |   |
| R. D.  | 21  | i    | i     | Spont.            | 4th                   | 150      | 4                       | Good    | Normal        |   |
| R. F.  | 30  | ii   | ii    | Spont.            | 4th                   | 90       | 3                       | Good    | Normal        |   |
| G. G.  | 30  | ii   | ii    | Spont.            | 3rd                   | 240      | 3                       | Good    | Normal        |   |
| G. G.  | 26  | i    | i     | Spont.            | 4th                   | 150      | 4                       | Good    | Normal        |   |
| Y. G.  | 28  | i    | i     | Spont.            | 3rd                   | 150      | 4                       | Good    | Normal        |   |
| G. G.  | 24  | ii   | ii    | Spont.            | 4th                   | 150      | 4                       | Good    | Normal        |   |
| B. G.  | 30  | ii   | ii    | Spont.            | 3rd                   | 150      | 4                       | Good    | Normal        |   |
| M. G.  | 25  | i    | i     | Spont.            | 3rd                   | 150      | 3                       | Good    | Normal        |   |
| B. II. | 23  | i    | i     | Elec. Cesarean    | 4th                   | 100      | 3                       | Fair    | Normal        | Small dose given Patient Med. Febrile                                 |

disease with prophylaxis against future infection or cancerous change. The "selling point" rests upon prevention of posthysterectomy stump carcinoma and cervicitis. Supravaginal hysterectomy possesses certain compensating advantages. It is done more rapidly and with little blood loss. There is less danger to the urinary structures and no drying or constriction of the vagina. Of first importance is the maintenance of adequate vaginal support by retaining the normal cervical fascial attachments, the keystone of the vaginal vault.

Published opinion on abdominal hysterectomy for fifteen years may be divided with some accuracy into (1) those favoring supravaginal hysterectomy, and (2) those relying mainly upon total hysterectomy.

Hochman, in an analysis of 1,114 supravaginal operations at the Woman's Hospital in New York, found three cases of stump cancer. Preoperative treatment of the cervix by conization or carbolization helped to prevent subsequent endocervicitis and lessened the development of stump cancer. While the occurrence of stump cancer did not warrant panhysterectomy with its greater mortality, every cervix should be inspected and definitely diseased cervical tissues should be thoroughly removed. Kostmayer concluded "since eventual mortality is the same for total hysterectomy, and supravaginal hysterectomy plus carcinoma in the remaining cervix, I prefer the deaths to come from the latter and give the years of intervening life to the patient. Leave the cervix, watch it, and treat it." Healy and Arneson studied 67 patients with stump carcinoma, and did not believe the low incidence justified the higher mortality of total hysterectomy. Seley, quoted by Sackett, found the mortality in 3,088 hysterectomies to be 2.3 per cent for the supravaginal and 3.98 per cent for the total operation, although Farrar, from the same clinic, favored total hysterectomy. From his own statistics, Joe Meigs believed cancer of the retained cervix as not more likely after subtotal hysterectomy, but half as likely, as in women as a whole. He advocated the total operation only where cervical repair or amputation was difficult and cauterization out of the question. He considers the cervixes of nullipara or patients with fibroids as especially bad, since a larger percentage of these developed stump cancer. Phaneuf and Belson favor the supravaginal operation, although stressing the need for selecting the operation to the condition of the patient and her age, and Bland in discussion agrees. Harris, reporting 739 cases, found the incidence of the total operation increasing, and carrying a persistently higher mortality than the supravaginal under similar elective conditions. Dannreuther generally favors supravaginal hysterectomy.

As against these selected views favoring supravaginal hysterectomy, there is formidable disagreement.

Baldwin (in discussion of Phaneuf) advises pan-hysterectomy "always," since he believes the cervix is useless and he records more than 40 cases of stump carcinoma after supravaginal hysterectomy. Gellhorn and Spain and Waldeyer advise routine complete hysterectomy and Von Graff, after collecting a large number of cases of stump carcinoma, is in agreement. Smith of Danforth's Clinic, in an analysis of 1,200 hysterectomies, had a lower mortality for the total operation, although

Masson, urging careful selection of cases, definitely believes that the total operation carries a higher mortality. In Faulkner's report on 1,544 cases, the mortality varied little in the different types of operations. Goodall has shifted his preference to the total operation, with no regrets. On the other hand, Murphy reported ureteral and bladder injuries ten times more frequent after complete hysterectomy than after supravaginal operations, where all cases were operated upon by well-trained men in a good hospital. Counsellor disbelieves the need for unfavorable sequelae to total hysterectomy, which he favors, and has described a technique to overcome them. Pearse performs total hysterectomy almost as a routine and Weir does a supravaginal hysterectomy only when complications are so extensive that panhysterectomy cannot be done with safety.

What conclusions may be drawn from such varied and conflicting opinions as to the relative safety and facility of total and supravaginal hysterectomy?

It would seem that in average and often in expert hands, the total operation carries greater morbidity and mortality for *comparable* cases, since it involves a more difficult and dangerous technique. An appeal from this statement may be found in many of the foregoing series which indicate that the mortality and morbidity rates of the complete and supravaginal operations do not materially differ. Reappraisal of most of these data will show the supravaginal procedure to have been followed when pelvic complicating factors made the complete operation either impossible or unreasonably hazardous. Comparing data of complete operations done in good risk cases with clean pelves, with supravaginal operations performed upon patients with huge tumors, extensive pelvic adhesions, coexisting endometriosis or residual pelvic inflammatory disease, is unconvincing statistical deception. It would seem better to admit the necessity and preference in given cases for the suitable and safe operation, which might be either.

Since the outstanding and apparently only accomplishment of total hysterectomy not possessed by the supravaginal operation, is the removal of a cervix which may postoperatively become the seat of cancer or infection, or is a distorted result of parturition, let us first consider recorded opinion on stump cancer.

As already noted, there is considerable difference of opinion regarding the frequency of stump cancer. Fahndrich collected 395 cases with an incidence of about 0.4 per cent. Von Graff's figures would indicate that 4 per cent of all cervical cancers are of the retained stump. Fricke and Bowing reported 57 stump carcinomas in 1676 cervical cancers or 3.4 per cent. Pearse's 34 cases of stump cancer represent 5.6 per cent of all cervical cancer seen. Healy and Arneson, Hann, Benda, and Hochman question a high cancer incidence in the retained stump. And when it does occur, there are varying opinions as to its relative danger. It was formerly believed that it was generally not far from hopeless when discovered, but Behney has recorded 67 cases with results of treatment no worse than in cervical cancer in general, and Ward agrees that results generally are better than in cervical cancer where no opera-

tion had been done. This he ascribes to the diminished cervical circulation and interference with lymphatic drainage.

For the unbiased, the dissimilarity in published experience reveals the status of stump carcinoma as highly unsettled. Whether the death incidence from stump carcinoma after supravaginal hysterectomy balances or overcomes the more unfavorable operative figures for the total operation is debatable. While cancer in a clean, retained cervix is a rarity, it nevertheless is a positive postoperative danger, entirely irrespective of the merits of controversial opinion as to its frequency.

Infection of the retained cervix is a more frequent sequel, always mentioned and immediately forgotten. It may cause no end of discomfort until treated and as a constant possibility it should receive due attention at operation.

Since cancer in the retained stump does occur, and since cervical infection develops on occasion when a total hysterectomy is either impossible or inadvisable, various methods have evolved for managing the cervix prior to performing supravaginal hysterectomy. The purpose of these several techniques is the removal or destruction of the cervical mucosa, by carbolization, by actual cautery, or by electric conization, as recommended by Hochman, Donay, Bland, Sutton, Kelly, Polak and others.

Cashman and Frank cauterized 82 per cent of cervixes prior to supravaginal hysterectomy in 1,464 cases, with a gross mortality of 1.91 per cent. Such a procedure may eliminate postoperative cervicitis, but can hardly prevent stump cancer where, as noted by Von Graff, over 80 per cent of these develop from the squamous cells of the vaginal portion. Miller and Todd in 1938 described a technique for cervical conization suitable for use prior to supravaginal hysterectomy and recorded favorable results in 899 cases. This experience was in accord with that of Stadiem who recommended it routinely with supravaginal hysterectomy and always where panhysterectomy might be hazardous.

For the past twelve years it has been my custom to do an electrocervicectomy prior to proposed or probable supravaginal hysterectomy. The technique consists in conization using a Bovie or similar current with a modified Hyam's loop, deep enough to remove all of the gland-bearing tissue of the endocervix. A wire loop then excises a large part of the portio vaginalis.

While epidermoid carcinoma arises characteristically at or near the margin of the external os, it may arise somewhat further from this margin, although this is uncommon in the recorded experience of those few men who have seen considerable numbers of early cervical cancers. It may possibly arise from the sites of squamous cell metaplasia seen in endocervical glands. An electrocervicectomy will remove all of these potential cancer or infection sites quickly, easily and safely.

In 18 of the cases where electrocervicectomy preceded total abdominal hysterectomy, postoperative sections made through the uterus

and coned area of the cervix showed the effectiveness of this technique in eliminating the danger zones.

It is not necessary to stress the value of a danger-free cervix as a support for the vaginal vault in maintaining vaginal depth, and in closing the opening in the pelvic fascial diaphragm. Any function the fibromuscular, mucosa-free cervical stump may possess in retarding atrophy of retained ovaries is admittedly dubious, but still theoretically possible.

#### PERSONAL SELECTION OF OPERATION

In 388 hysterectomies\* reviewed there were 83 vaginal hysterectomies, with results as previously noted. Of the other 305 cases, 208 were supravaginal hysterectomies, of which 94 had associated vaginal plastic operations. One hundred fourteen or 55 per cent of these supravaginal hysterectomies were preceded by electrocervicectomy. The morbidity in the 208 cases was 16.2 per cent. There were 4 deaths with a mortality of 1.9 per cent. One death followed forty-eight hours after injudicious electrocervicectomy for infected cervical polyp prior to supravaginal hysterectomy. One patient died from transfusion reaction 6 hours post-operatively. One died from peritonitis and one from pulmonary embolism. Ninety-seven total hysterectomies were performed.

In three cases, conditions made the immediate removal of the diseased cervix unduly hazardous. The uterus was removed supravaginally, and then the cervical stump grasped with a crossed tenaculum inserted into the canal. This was used to lift and manipulate the cervix while its isolation and excision was completed. There were no deaths in the total hysterectomy cases. The morbidity was 20.4 per cent. No ureters are known to have been injured. One patient developed intestinal obstruction six weeks postoperatively, successfully corrected by operation. Three cases developed marked thrombophlebitis of the lower extremities.

The intent of this presentation is not to array overwhelming statistical minutia. It represents a smaller, personally operated-upon and cared-for group. Therefore, while admitting numerical limitations and with no attempt to rival many excellent and exhaustive analyses already on record, it is felt that this personal study constitutes a basis for discerning analysis sufficient to justify the views expressed concerning operation selection.

#### CONCLUSIONS

Hysterectomy for nonmalignant uterine disease should be a selective operation, with the choice resting upon condition of patient and pathology, for the best immediate and ultimate outcome to the patient.

The vaginal route is preferred for patients with ample vagina, or with descent at least equivalent to a second-degree prolapse, and only moderate uterine enlargement. It is the choice where hysterectomy is indicated in the old, the obese, the debilitated.

When abdominal hysterectomy is planned, the total operation is the *preferred* technique unless the patient has a very deep pelvis,

\*Personally operated private and service cases at Christ and Fairmount Hospitals.

a short vagina or the size of the pelvic tumor or associated pelvic pathology introduce risks out of proportion to the dangers inherent in a residual cervical stump. It is always preferable, although not always possible, to remove a badly distorted cervix with the uterus, rather than perform a plastic operation upon it.

Supravaginal hysterectomy is the *safer* technique for removing the uterus where pelvic conditions make the operation slow, sanguineous or dangerous. The hazards of posthysterectomy cervical stump cancer or infection can be removed effectively by combining radical cervical conization, or electrocervicectomy with supravaginal hysterectomy. This vaginal-abdominal approximation of total hysterectomy, leaving a fibromuscular cuff of cervix, combines the advantages of both total and supravaginal operations and possesses the disadvantages of neither. It is recommended as a safer procedure in average hands than a total hysterectomy for all cases, and as a safer procedure even in expert hands, than total hysterectomy in "bad risk pelves."

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## DISCUSSION

DR. EDWARD H. RICHARDSON, BALTIMORE, Md.—This paper of Dr. Waters brings before the Society very properly an annual topic of discussion. With most of his thesis I am in complete agreement. The title very properly indicates that there is no established procedure for removing the uterus that is equally applicable to all cases.

I would like to recommend in suitable cases substitution for vaginal hysterectomy the operation which I published about five years ago under the title of "composite operation," which owes its existence to the fact that I have been repeatedly confronted by patients upon whom total vaginal hysterectomy had been performed by other surgeons and later developed varying degrees of vaginal prolapse, enterocele, cystocele, et cetera. I endeavored to discover what factors in the several operative procedures now widely employed were responsible for these recurrences and failures, and the composite operation was constructed upon the foundations of that analysis. I simply eliminated from the established procedures those factors which I considered responsible for the failures, and then combined those steps which time had proved to be dependable.

Our experience for the past five years with this operation has convinced me of the superiority of it over total vaginal hysterectomy as a reconstructive procedure for many combinations of vaginal hernias. Certainly it does not seem reasonable routinely to employ total vaginal hysterectomy in this type of case if we focus our attention for a moment upon the importance of the upper pelvic floor as the chief support of the pelvic viscera. I conceive of this anatomic structure as composed simply of two suspension bridges constructed at right angles to each other, the cardinal ligaments constituting the transverse bridge, while the pubocervical fascia in front together with the uterosacral ligaments posteriorly are the chief components of the anteroposterior bridge. Both of these bridges owe their mechanical efficiency as supporting structures mainly to the fact that they are firmly anchored into a small segment of the cervix at the level of and adjacent to the internal os. In a total vaginal hysterectomy the first thing you do is to crush these structures with a clamp, then divide them. You then further impair their circulation by suturing them together. The result is a number of recurrent vaginal hernias. The composite operation by contrast safeguards the vital keystone, that little upper segment of the cervix together with its fascial supports, but removes the two portions of the uterus in which carcinoma occurs; namely, the corpus above the level of the internal os and the diseased part of the cervix below the cardinal ligaments. This plan also greatly diminishes the danger of damage to the ureters. By preserving the upper pelvic floor intact adequate support for correction of associated types of hernia is provided in accordance with sound surgical principles. Our results are certainly convincing so far as the ultimate outcome of these cases is concerned. The operation does require patience and accurate knowledge of the anatomy. Nobody but an experienced operator should undertake it. It is more time consuming too, but the end results are far superior to the other types of operation now in general use for the treatment of uterine prolapse and associated vaginal hernias.

Concerning the controversy of total versus subtotal abdominal hysterectomy, I do not see why there should be any difference of opinion about the desirability of removing every diseased cervix. Unfortunately, often there is some contraindication for so doing, and the operator is compelled to perform a subtotal operation and knowingly to leave a diseased cervix. On the other hand I have been unable, in following the literature of the last few years, to find a single convincing reason that would justify the routine removal of normal cervixes.

I think the arguments that have been built up on the incidence of stump cancer, for example, are totally fallacious. I know of no work that has been done to

show the actual incidence of stump cancer in normal cervixes that were left behind. Surely there is every reason to believe that the vast majority of stump cancers have occurred in cases where subtotal operations were done because the complicated pathology encountered or the patient's condition, or the limited experience and skill of the operator, did not warrant the more radical procedure, and a diseased cervix was left untreated. In my entire experience I have seen only one instance of stump cancer where I left a normal cervix. I do not believe, therefore, that routine removal of the normal uterine cervix should be done. Total abdominal hysterectomy is certainly a more dangerous and more hazardous operation from the standpoint of morbidity as well as of mortality, as will immediately become evident if analysis is made of equally severe grades of pathology treated by the two methods. Otherwise, how can you explain, for example, the paper presented today on the incidence of urinary tract fistulas following this operation?

I believe it is a very unfortunate thing that this Society still remains divided in opinion on this matter and I think it is a dangerous teaching to go out into the country that surgeons who are less competent than this group of men should routinely do total abdominal hysterectomy even though the cervix is normal. I am emphatically opposed to this teaching and practice.

DR. N. SPROAT HEANEY, CHICAGO, ILL.—I agree with the author of this paper that no routine operation should be performed in all cases, but the operation should be adapted to the case at hand. A trained gynecologist should be able to do a complete abdominal or a vaginal hysterectomy with as much ease and familiarity as a supravaginal hysterectomy. A supravaginal hysterectomy should not be the choice of an operator because he cannot do a vaginal hysterectomy or complete abdominal hysterectomy. The advantage of a vaginal hysterectomy is apparent, when I say that the number of vaginal hysterectomies, since we began the use of ethylene, now totals, 1,056 completed cases with only 3 deaths.

One objection to a vaginal hysterectomy which is often mentioned is shortening of the vagina. If one performs vaginal hysterectomies only for prolapse, I can see why that idea arises, for in such cases, the vagina is always shortened because the caliber of the tube has been increased. When the vagina is of normal length to begin with, no shortening occurs. If the vagina is incised at the same place, I cannot see why removing the uterus from below will shorten the vagina more than if it is removed from above. Logically the vagina should be shortest after a supravaginal hysterectomy because the retained cervix detracts from the length of the vagina.

If I am not going to take the cervix out I leave it strictly alone. I do not believe it should be burned or excoriated, because you cannot do either of these things and not have it invaded by the flora of the vagina and thus have an infected cervix. If you add cauterization of the cervix to a supravaginal hysterectomy, I think you are courting serious trouble.

DR. JOE V. MEIGS, BOSTON, MASS. (By invitation).—Three of my patients have had cancer of the cervical stump following supravaginal hysterectomy and I had to explain to them that at operation I had left the cervix in and that I did not take it out because it was a difficult procedure. Since I have been at the Pondville Hospital, out of 1,200 cases of cancer of the cervix seen there we have had 100 cancers of the cervical stump. Many of these cancers were doubtless present at the time of their supravaginal hysterectomy and some developed cancer many years afterward. Because of 3 cases occurring in my own patients and of seeing 100 cases at the State Hospital, I advocate removal of the cervix wherever possible.

About 10 per cent of our cases of cancer of the cervix occurred in nulliparas. I do not believe one can tell when a cervix may develop cancer. I feel sure that from now on whenever possible I will do a total hysterectomy until I am taught differently by my own experience.



DR. GEORGE GRAY WARD, NEW YORK, N. Y.—I would like to endorse what Dr. Meigs has just said as I heartily agree with his point of view. In my clinic at the Woman's Hospital in 1940 we found that about 7 per cent (6.9 per cent) of the 879 cases of cervical cancer had cancer of the stump. We also have had nulliparas among that number. I believe that the entire uterus should be removed provided it will not be a matter of undue risk to the patient. The total operation is preferable because of the evident higher incidence of stump cancer than was formerly thought to occur, and of the frequent association of cancer with fibroids. Conization or cauterization of the cervical canal is no safeguard as 80 per cent of cancers of the cervix originate on the portio vaginalis.

DR. WILLIAM P. HEALY, NEW YORK, N. Y.—I have had in my private practice a large group of patients returning to me for annual examinations. In all those years I have had only two instances where cancer has developed in the cervix remaining after a supravaginal hysterectomy done by me.

One of these occurred in a woman who had had a supracervical hysterectomy in her early forties. Except for the uterine myomas, she had been in excellent health, had never conceived, and had a perfectly normal cervix. She later came to me with vaginal spotting. The cervical lesion was less than 1 cm. in size and noninfiltrating, but coincidentally she had a large pulmonary carcinoma. We assumed the cancer in the lung developed first but that we were dealing with an instance of double primary carcinoma.

At the Memorial Hospital Dr. Arneson and I went over about 1,000 cases and we found that only 2 per cent of our cases were bona fide stump carcinomas, in which epidermoid carcinoma had developed in the cervix.

I feel therefore as Dr. Richardson does, that for us to recommend panhysterectomy just because we are removing the corpus when the patient has a normal clean unlacerated and uninfected cervix, is carrying the argument further than we really need to do, especially if you are following up these patients and looking after their general health.

DR. CURTIS F. BURNAM, BALTIMORE, MD.—Dr. Howard Jones of the Kelly Clinic has recently reviewed 900 consecutive cases of carcinoma of the cervix. Excluding those sent for prophylactic radiation after panhysterectomy and those treated by radium elsewhere before coming to us, there remained approximately 700 cases. Among these 700 cases, 51 were carcinomas of the stump or 7 per cent. Of these 51 cases, however, 16 had developed within two years of the supravaginal hysterectomy. It seems only fair therefore to assume that these cancers may have been present at the time of the operation. This leaves us 35 cases or about 5 per cent.

I realize that one cannot calculate the occurrence of cancer of the cervix after supravaginal hysterectomy from such material. The only conclusive way for this to be done would be to go over a very large series of supravaginal hysterectomies. It seems to me this could be easily done if a dozen of the big clinics would cooperate to do this work for us.

It is evident that before doing any gynecologic operation, much less a hysterectomy, that a thorough examination of the patient should be made under gas with biopsy from the cervix, curettage and all other methods of diagnosis utilized. To be able simply to look at a cervix and tell positively whether it is precancerous or not is beyond my powers of diagnosis.

DR. SAMUEL A. COSGROVE, JERSEY CITY, N. J.—I believe that our thinking would be straighter if we expressed ourselves in the same way. Dr. Meigs and several other speakers have said that they found cancer of the cervical stump in 7 or 8 per cent of the cases observed after supravaginal hysterectomy. Those who approached the subject from the other end and surveyed their hysterectomies, found 2 per cent or less of stump cancer. We cannot come to a common understanding

unless we get our facts lined up on the same basis. Those who have recorded series of cases of cancers of the cervix say nothing about the incidence of hysterectomy in the general population of which 8 per cent of carcinoma of the cervix represents a cross section. I think this whole problem might better be turned over to statisticians rather than gynecologists.

DR. E. H. RICHARDSON, BALTIMORE, MD.—I cannot see that the incidence even of 7 per cent of stump cancers reported from some clinics has any bearing on the position that I have taken. This position is, that when a cervix is diseased it should either be removed with the uterus or at a second operation, and when normal it should not be removed. Is there any basis whatsoever upon which you can pick out of the stump cancers those cases that developed in normal cervices? Is it not obviously absurd to assume that all of these cervices were normal when the subtotal operation was done? Certainly it is far more rational to assume that they were left because of extensive pelvic disease that precluded judicious use of total hysterectomy. If so, one must conclude that these cervices also were diseased and were left untreated later to supply the 7 per cent incidence of stump cancers now being fallaciously put forward in advocacy of routine removal of normal cervices.

DR. WATERS (closing).—I will answer one question specifically, as to when electrocervicectomy was used. It was done immediately before the operation if the cervix was not acutely infected. It preceded operation when a total hysterectomy seemed impossible because of some existing condition. Infected cervices were treated weeks in advance of operation.

As to stump cancer, I found the differences of opinion essentially the same fifteen years ago as expressed here. Even with total excision of the uterus, one will occasionally find later a cancer of the vault, so that you still cannot completely escape it.

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With deep regret we announce the death of Dr. Charles Virgil Mosby, Chairman of the Board of The C. V. Mosby Company, St. Louis, on Monday, November 9, 1942.

His vision and courage will continue as an inspiration throughout the future of the company that he founded.

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# Items

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## American Board of Obstetrics and Gynecology

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Saturday, February 13, 1943, at 2:00 P.M.

Arrangements will be made so far as possible for candidates in military service to take the Part I examination (written paper and submission of case records) at their places of duty, the written examination to be proctored by the Commanding Officer (medical) or some responsible person designated by him. Material for the written examination will be sent to the proctor several weeks in advance of the examination date. Candidates for the February 13, 1943, Part I examination, who are entering military service, or who are now in service and may be assigned to foreign duty, may submit their case records in advance of the above date, by forwarding the records to the Office of the Board Secretary. All other candidates should present their case records to the examiner at the time and place of taking the written examination.

The Office of the Surgeon-General (U. S. Army) has issued instructions that men in service, eligible for Board examination, be encouraged to apply and that they may request orders to Detached Duty for the purpose of taking these examinations whenever possible.

All candidates will be required to take both the Part I examination, and the Part II examination (oral-clinical and pathology examination). Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held later in the year.

The Part II examination will be held at Pittsburgh, Pennsylvania, from May 19-25, 1943. Notice of the exact time and place of the examinations will be sent all candidates well in advance of the examination date. Candidates in Military or Naval Service are requested to keep the Secretary's Office informed of any change in address.

If a candidate in Service finds it impossible to proceed with the examinations of the Board, deferment without time penalty will be granted under a waiver of our published regulations applying to civilian candidates.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

## American College of Surgeons Cancels Clinical Congress

The annual clinical Congress of the American College of Surgeons which was scheduled to be held in Cleveland, Nov. 17-20, 1942, was canceled by the Board of Regents of the College at a meeting held in Chicago, Wednesday morning, October 14.

|                |          |           |           |                               |            |            |        |              |                         |                                    |
|----------------|----------|-----------|-----------|-------------------------------|------------|------------|--------|--------------|-------------------------|------------------------------------|
| H. H.          | 34<br>38 | iii<br>ii | iii<br>ii | Spont.<br>Premature<br>5½ mo. | 3rd<br>3rd | 240<br>150 | 4<br>3 | Good<br>Good | Normal<br>Normal        |                                    |
| M. I.<br>V. M. | 26<br>27 | i<br>i    | i<br>i    | Spont.<br>Breech              | 3rd<br>7th | 150<br>150 | 3<br>4 | Good<br>Good | Normal<br>Normal        | Nursed until sixth<br>day          |
| H. M.<br>P. M. | 27<br>24 | ii<br>i   | ii<br>ii  | Spont.<br>Spont.              | 3rd<br>4th | 150<br>150 | 4<br>4 | Good<br>Good | Subinvolution<br>Normal |                                    |
| R. M.          | 28       | i         | i         | Breech                        | 3rd        | 150        | 4      | Good         | Normal                  |                                    |
| M. N.          | 21       | i         | i         | Spont.                        | 6th        | 150        | 3      | Good         | Normal                  |                                    |
| P. N.          | 30       | i         | i         | Spont.                        | 3rd        | 150        | 4      | Good         | Normal                  | Filled in again<br>after last dose |
| P.             | 28       | ii        | ii        | Spont.                        | 3rd        | 150        | 3      | Poor         | Normal                  |                                    |
| D. S.          | 31       | ii        | ii        | Spont.                        | 3rd        | 150        | 4      | Good         | Normal                  |                                    |
| I. S.          | 23       | i         | i         | Spont.                        | 4th        | 90         | 4      | Good         | Normal                  |                                    |
| S.             | 21       | i         | i         | Premature<br>5½ mo.           | 3rd        | 180        | 3      | Fair         | Good                    | Mod. hirsutism                     |
| II. S.         | 32       | ii        | ii        | Spont.                        | 4th        | 150        | 4      | Fair         | Normal                  |                                    |
| M. S.          | 23       | i         | i         | Spont.                        | 4th        | 150        | 3      | Good         | Normal                  |                                    |
| L. S.          | 29       | ii        | ii        | Spont.<br>(Hydram.)           | 4th        | 90         | 3      | Good         | Normal                  |                                    |
| P. S.          | 21       | i         | i         | Spont.                        | 5th        | 120        | 4      | Good         | Good                    |                                    |
| T. T.          | 26       | i         | i         | Low forceps                   | 3rd        | 150        | 3      | Good         | Good                    |                                    |
| L. T.          | 30       | i         | i         | Spont.                        | 3rd        | 90         | 3      | Good         | Normal                  |                                    |
| L. T.          | 28       | ii        | ii        | Breech                        | 3rd        | 150        | 4      | Good         | Normal                  |                                    |
| V.             | 27       | i         | i         | Spont.                        | 3rd        | 150        | 2      | Good         | Normal                  |                                    |
| L. V.          | 24       | ii        | ii        | Spont.                        | 3rd        | 150        | 4      | Good         | Normal                  |                                    |
| J. W.          | 30       | iii       | iii       | Spont.                        | 4th        | 60         | 3      | Good         | Normal                  | Temp. relief while<br>nursing      |
| J. W.          | 28       | ii        | ii        | Spont.                        | 4th        | 150        | 3      | Good         | Normal                  |                                    |
| M. W.          | 40       | i         | i         | Midforceps                    | 5th        | 150        | 3      | Good         | Normal                  |                                    |
| B. Z.          | 20       | i         | i         | Spont.                        | 4th        | 150        | 3      | Good         | Subinvolution           |                                    |

CROOKS, PHILIP E., Blood transfusion reaction due to intra-group incompatibility, 121

CUYLER, W. KENNETH, (WITH HAMBLIN, E. C., AND BAPTIST, MARGARET), Pregnanediol determinations in gynecology and obstetrics, 442

## D

DANFORTH, W. C., Presidential address at annual meeting of American Gynecological Society, 743

DANIEL, MARK, AND ANTIS, MAX, Macrocytic hyperchromic anemia of pregnancy, 93

DANNREUTHER, WALTER T., Partial congenital aplasia of vagina, 1063

DAVIS, IONA F., (WITH DOUGLAS, R. GORDON, AND SHANDORF, JAMES F.), Gonorrhea in female and its treatment with sulfonamides, 1026

DE BARENNE, DOROTHEA DUSSER, AND GIBBS, FREDERIC A., Variations in electroencephalogram during menstrual cycle, 687

DERBRUCKE, MAURICE G., (WITH JACOBY, ADOLPH), Vaginal iontophoresis of choline compound, 250

D'ESOP, D. ANTHONY, AND MARCHETTI, ANDREW ANTHONY, Causes of fetal and neonatal mortality, 1

DICKINSON, KENNETH, AND PROCTER, IVAN M., Comparative measurements of female pelvis, 585

DIDDLE, A. W., AND MCKEE, A. P., Urinary infection in pregnancy due to flexner dysenteriae, 481

—, AND PLASS, E. D., Mortality of prematurely born infants, 279

DIECKMANN, WILLIAM J., AND KHARASCH, MORRIS S., Solution of posterior pituitary sulfonate (pit-sulfonate) in labor, 820

DIEHL, WILLIAM K., (WITH HUNDLEY, J. MASON, JR., AND DIGGS, EVERETT S.), Hormonal influences upon ureter, 858

DIGGS, EVERETT S., (HUNDLEY, J. MASON, JR., AND DIEHL, WILLIAM K.), Hormonal influences upon ureter, 858

DILL, L. V., (WITH ROBINSON, C. E., CADDEN, J. F., AND ISENHOUR, C. E.), Glomerular filtration and renal blood flow in hypertensive woman and in posttoxicemic hypertension, 616

—, ISENHOUR, C. E., CADDEN, J. F., AND ROBINSON, C. E., Glomerular filtration and renal blood flow in "normal" patients following toxemias of pregnancy, 66

DOCKERTY, MALCOLM B., (WITH MURRAY, NELSON A., AND PEMBERTON, JOHN DEJ.), Unusual coexistence of granulosa cell tumor and ovarian teratoma containing thyroid tissue, 134

—, AND CRAIG, WINCHELL MCK., Chorion-epithelioma, 497

DORSEY, CHARLES W., Placental polyp with severe late puerperal hemorrhage, 591

DOUGLAS, R. GORDON, DAVIS, IONA F., AND SHANDORF, JAMES F., Gonorrhea in female and its treatment with sulfonamides, 1026

DUCKMAN, S., AND TURINO, T. R., Use of methyl testosterone for relief of breast engorgement in puerperium, 112

## E

EASTMAN, N. J., (WITH MANAHAN, C. P., AND CONNALLY, H. F., JR.), Experience of Johns Hopkins Hospital with cesarean section, 999

EICHNER, EDUARD, (WITH BISKIND, LEONARD H.), Apparatus for resuscitation of newborn infants, 147

EISELE, C. WESLEY, TUCKER, WILLIAM B., VINES, ROBERT W., AND BATTY, JOHN L., Problem of unsuspected tuberculosis in pregnancy, 183

ERVING, HENRY W., Pseudomyxoma peritonei, 492

EVANS, WILLIAM B., SICKEL, GEORGE B., AND IVINS, JOSEPH L., Primary ovarian pregnancy, 528

EVERETT, HOUSTON S., AND SCOTT, ROGER B., Possible etiologic role of gynecologic lesions in production of hypertension, 1010

## F

FALLS, FREDERICK H., BERNELL, EDWARD C., AND KOBAK, DISRAELI, Conservative treatment of pelvic inflammation with Newman thermoflo, 240

FERGUSON, A. DREW, (WITH VELKOFF, ABRAHAM S.), Bilateral dry gangrene of both lower extremities due to ergot, 331

FIDLER, ROSWELL S., (WITH SILBERNAGEL, WYNNE M.), Ante-partum rupture of umbilical vein, 712

FINESINGER, JACOB E., MEIGS, JOE V., AND SULKOWITZ, HIRSH W., Clinical, psychiatric and psychoanalytic study of case of male pseudohermaphroditism, 310

FISCHER, HENRY S., AND KANTROWITZ, A. R., Sarcoma botryoides of cervix, 141

FRALIN, FLORENCE G., (WITH WILLIAMS, PHILIP F.), Nutrition study in pregnancy, 647

FRANK, IRVING L., AND GEIST, SAMUEL H., Postmenopausal endometriosis, 652

FRIDAY, RUPERT H., (WITH BEECHAM, CLAYTON T.), Adenocarcinoma with ovarian metastases, 512

—, (WITH BEECHAM, CLAYTON T.), Comparative local tissue reaction and styptic action of sulfanilamide, 88

## G

GEIST, SAMUEL H., (WITH FRANK, IRVING L.), Postmenopausal endometriosis, 652

GETZOFF, PAUL L., (WITH ARNELL, RUPERT E.), Renal ureteral calculi in pregnancy, 34

GIBBS, FREDERIC A., (WITH DE BARENNE, DOROTHEA DUSSER), Variations in electroencephalogram during menstrual cycle, 687

—, AND REID, DUNCAN E., Electroencephalogram in pregnancy, 672

GINZLER, ARTHUR M., AND CHESNER, CHARLES, Toxic manifestations in newborn infant following placental transmission of sulfanilamide, 46

GLASS, SAMUEL, (WITH MARX, RUDOLPH, AND SHULMAN, ALEX.), Experimentally produced fibroids in guinea pig and their possible analogy to myomas in human being, 259

# INDEX TO VOLUME 44

## AUTHORS INDEX\*

### A

- ALDRIDGE, ALBERT H., Intestinal injuries resulting from irradiation treatment of uterine carcinoma, 833
- , Transplantation of fascia for relief of urinary stress incontinence, 398
- ALEXANDER, F. A. D., AND MARTIN, CHARLES E., Simple apparatus for resuscitation of newborn, 351
- ALLEN, WILLARD M., AND HECKEL, GEORGE P., Effect of progesterone in adolescent girls and young women with functional uterine bleeding, 984
- ANTIS, MAX, (WITH DANIEL, MARK), Macrocytic hyperchromic anemia of pregnancy, 93
- ARNELL, RUPERT E., AND GETZOFF, PAUL L., Renal ureteral calculi in pregnancy, 34

### B

- BAPTIST, MARGARET, (WITH HAMBLE, E. C., AND CUYLER, W. KENNETH), Pregnanediol determinations in gynecology and obstetrics, 442
- BARROW, WOOLFOLK, AND MAXWELL, E. S., Tuberculosis of vulva, 145
- BARTHOLOMEW, R. A., Utopian obstetrics, 553
- BATTY, JOHN L., (WITH EISELE, C. WESLEY, TUCKER, WILLIAM B., AND VINES, ROBERT W.), Problem of unsuspected tuberculosis in pregnancy, 183
- BECK, ALFRED C., Detailed technique of modified local anesthesia for cesarean section, 558
- BEECHAM, CLAYTON T., AND FRIDAY, RUPERT H., Adenocarcinoma with ovarian metastases, 512
- , AND —, Comparative local tissue reaction and styptic action of sulfanilamide, 88
- BENNETT, HENRY G., JR., Methods for objective evaluation of estrogen therapy in menopause, 296
- BERNELL, EDWARD C., (WITH FALLS, FREDERICK H., AND KORAK, DISRAELI), Conservative treatment of pelvic inflammation with Newman thermo-flo, 240
- BIBB, JOHN D., Use of sulfanilamide powder in gynecologic and obstetric operations, 464
- BICKERS, WILLIAM, Puerperal uterine contractions, 581
- BIEREN, ROLAND E., AND COMPTON, BEVERLEY C., Estrogenic properties of dihydrostilbestrol (hexestrol), 287
- BISKIND, LEONARD H., AND EICHNER, EDUARD, Apparatus for resuscitation of newborn infants, 147

- BLAND, HARVEY G., (WITH PAYNE, WALTER R.), Anencephalus (with acute hydramnios) diagnosed by x-ray, 593
- BOSSERT, LESTER J., Bilateral ovarian carcinoma associated with intrauterine pregnancy, 336
- BOURGEOIS, GEORGE A., Identification of fetal squamas and diagnosis of ruptured membranes by vaginal smear, 80
- BREWER, JOHN I., Studies of human corpus luteum, 1048
- BRODERS, ALBERT C., (WITH WROCK, DONALD H.), Adenomyosis of Fallopian tube, 412
- BRODY, SIMON, Fibroma of ovary, 521
- BURR, H. S., (WITH LANGMAN, LOUIS), Electrometric timing of human ovulation, 223
- BUNTON, C. L., Use of estrogens in treatment of leucoplakia, kraurosis, and senile vaginitis, 109

### C

- CADDEN, J. F., (WITH ROBINSON, C. E., DILL, L. V., AND ISENHOUR, C. E.), Glomerular filtration and renal blood flow in hypertensive woman and in posttoxic hypertention, 616
- , (WITH DILL, L. V., ISENHOUR, C. E., AND ROBINSON, C. E.), Glomerular filtration and renal blood flow in "normal" patients following toxemias of pregnancy, 66
- CARTER, BAYARD, Bacteriologic study of pyometra, 1071
- CARTWRIGHT, EAKLE W., (WITH WATERS, EDWARD G., AND LYNCH, J. EDWARD), Immediate post-partum repair of old perineal lacerations, 124
- CHESNER, CHARLES, (WITH GINZLER, ARTHUR M.), Toxic manifestations in newborn infant following placental transmission of sulfanilamide, 46
- COMPTON, BEVERLEY C., (WITH BIEREN, ROLAND E.), Estrogenic properties of dihydrostilbestrol (hexestrol), 287
- CONNALLY, H. F., JR., (WITH MANAHAN, C. P., AND EASTMAN, N. J.), Experience of Johns Hopkins Hospital with cesarean section, 999
- CORBIN, HAZEL, Prepared parents—the core of creative family living, 166
- COURTIS, MORRIS, Ruptured ovarian pregnancy, 128
- CRAIG, WINCHELL McK., (WITH DECKER, MALCOLM B.), Chorionepithelioma, 497

\*July, pp. 1-182; August, pp. 183-366; September, pp. 367-552; October, pp. 553-742; November, pp. 743-924; December, pp. 925-1134.

LONGWELL, F. H., (WITH TRUSSELL, RAY E., WILSON, MARY E., AND LAUGHLIN, K. A.), Vaginal trichomoniasis, 292

LYNCH, J. EDWARD, (WITH WATERS, EDWARD G., AND CARTWRIGHT, EAKLE W.), Immediate post-partum repair of old perineal lacerations, 124

## M

MANAHAN, C. P., CONNALLY, H. F., JR., AND EASTMAN, N. J., Experience of Johns Hopkins Hospital with cesarean section, 999

MANN, BERNARD, MERANZE, DAVID R., AND LEIB, J. GOLUB, Histopathologic diagnoses of atypical endometrium, 460

MARCHETTI, ANDREW ANTHONY, (WITH D'ESOP, D. ANTHONY), Causes of fetal neonatal mortality, 1

MARTIN, ARTHUR C., (WITH HUGHES, WENDELL L.), Treatment of hyperemesis gravidarum with intramuscular injections of husband's blood, 103

MARTIN, CHARLES E., (WITH ALEXANDER, F. A. D.), Simple apparatus for resuscitation of newborn, 351

MARX, RUDOLPH, GLASS, SAMUEL, AND SHULMAN, ALEX., Experimentally produced fibroids in guinea pig and their possible analogy to myomas in human being, 259

MASON, LYMAN W., Spontaneous abortion and its treatment with progesterone, 630

MASSEY, WARREN E., (WITH WILLIS, RAYMOND S., WINN, WATT W., MORRIS, A. TRUETT, AND NEWSOM, A. A.), Clinical observations in treatment of nausea and vomiting in pregnancy with vitamins B<sub>1</sub> and B<sub>6</sub>, 265

MAXWELL, E. S., (WITH BARROW, WOOLFOLK), Tuberculosis of vulva, 145

McKEE, A. P., (WITH DIDDLE, A. W.), Urinary infection in pregnancy due to Flexner dysenteriae, 481

MEIGS, JOE V., (WITH FINESINGER, JACOB E., AND SULKOWITZ, HIRSH W.), Clinical, psychiatric and psychoanalytic study of case of male pseudohermaphroditism, 310

MENDELSON, CURTIS L., AND PARDEE, HAROLD E. B., Pulse and respiratory rates during labor as guide to onset of cardiac failure in women with rheumatic heart disease, 370

MENGERT, WILLIAM F., Morphine sulfate as obstetric analgesic, 888

—, AND PAUL, WILLIAM D., Artificial pyrexia in pregnant women, 702

MERANZE, DAVID R., (WITH MANN, BERNARD, AND GOLUB, LEIB J.), Histopathologic diagnoses of atypical endometrium, 460

MILLER, NORMAN F., Surgical treatment and postoperative care of vesicovaginal fistula, 873

MILNOR, G. C., AND TILDEN, I. L., Endometrial cyst of groin associated with decidual reaction in appendix, 324

MOLOY, HOWARD C., Studies on head molding during labor, 762

MORRIS, A. TRUETT, (WITH WILLIS, RAYMOND S., WINN, WATT W., NEWSOM, A. A., AND MASSEY, WARREN E.), Clinical observations in treatment of nausea and vomiting in pregnancy with vitamins B<sub>1</sub> and B<sub>6</sub>, 265

MORTARA, FRANK, (WITH GREENBLATT, ROBERT B., AND TORPIN, RICHARD), Sexual libido in female, 658

MORTON, DANIEL G., Observations of development of pelvic conformation, 799

MURPHY, DOUGLAS P., Relation between uterine activity and reactivity to posterior pituitary extract during pregnancy, 117

—, Uterine tonus during labor, 694

MURRAY, NELSON A., DOCKERTY, MALCOLM B., AND PEMBERTON, JOHN DEJ., Unusual coexistence of granulosa cell tumor and ovarian teratoma containing thyroid tissue, 134

## N

NEWSOM, A. A., (WITH WILLIS, RAYMOND S., WINN, WATT W., MORRIS, A. TRUETT, NEWSOM, A. A., AND MASSEY, WARREN E.), Clinical observations in treatment of nausea and vomiting in pregnancy with vitamins B<sub>1</sub> and B<sub>6</sub>, 265

## P

PALMER, ALLAN, Cyclical estrogen therapy, 56

PARDEE, HAROLD E. B., (WITH MENDELSON, CURTIS L.), Pulse and respiratory rates during labor as guide to onset of cardiac failure in women with rheumatic heart disease, 370

PARKS, JOHN, AND SWEET, LEWIS K., Does antenatal use of vitamin K prevent hemorrhage in newborn infant? 432

PAUL, WILLIAM D., (WITH MENGERT, WILLIAM F.), Artificial pyrexia in pregnant women, 702

PAYNE, WAVERLY R., AND BLAND, HARVEY G., Anencephalus (with acute hydranmios) diagnosed by x-ray, 593

PEALE, AUGUSTIN R., Bilateral Brenner tumor of ovary, 138

PEEPLES, W. J., (WITH TORPIN, RICHARD, AND PUND, EDGAR), Etiologic and pathologic factors in series of 1,741 fibromyomas of uterus, 569

PEMBERTON, JOHN DEJ., (WITH MURRAY, NELSON A., AND DOCKERTY, MALCOLM B.), Unusual coexistence of granulosa cell tumor and ovarian teratoma containing thyroid tissue, 134

PHILLIPS, E. W., Allergic shock caused by synapoidin, 706

PLASS, E. D., (WITH DIDDLE, A. W.), Mortality of prematurely born infants, 279

PLATZ, CHARLES P., (WITH REYCRAFT, J. L.), Incidence of placenta previa during a ten-year period at Cleveland Maternity Hospital (1931-1940), 509

POLLARD, W. E., AND HELLENDALL, H., Death due to intraperitoneal rupture of strictured lymphogranulomatous rectum during parturition, 317

POSNER, LEWIS B., (WITH PULVER, MICHAEL), Colostrum test for pregnancy in prenatal clinic, 690

PRIDE, C. B., AND RUCKER, M. PIERCE, Eclampsia and ovarian pregnancy, 575

PROCTER, IVAN M., (WITH DICKINSON, KENNETH), Comparative measurements of female pelvis, 585

- GOLUB, LEIB J., (WITH MANN, BERNARD, AND MERANZE, DAVID R.), Histopathologic diagnoses of atypical endometrium, 460
- GOODWIN, ROBERT H., Bilateral ovarian dermoid cysts complicating pregnancy treated by bilateral oophorectomy, 525
- GREENBLATT, ROBERT B., MORTARA, FRANK, AND TORPIN, RICHARD, Sexual libido in female, 658
- GREENHILL, J. P., Use and potency of synthetic estrogens, 475
- GRUENWALD, PETER, Origin of endometriosis from mesenchyme of celomic walls, 470

## H

- HAMBLIN, E. C., CUYLER, W. KENNETH, AND BAPTIST, MARGARET, Pregnandiol determinations in gynecology and obstetrics, 442
- HAMILTON, EUGENE G., (WITH VOGT, WILLIAM H., JR.), Statistical study of 500 consecutive abdominal hysterectomies, 723
- HARRIS, JOSEPH, (WITH KROHN, LEON, AND HECHTER, OSCAR), Sources of error in detection of ovulation, 213
- HARTMAN, CARL G., Contributions of studies on primate animals, 156
- HECHTER, OSCAR, (WITH KROHN, LEON, AND HARRIS, JOSEPH), Sources of error in detection of ovulation, 213
- HECKEL, GEORGE P., (WITH ALLEN, WILLARD M.), Effect of progesterone in adolescent girls and young women with functional uterine bleeding, 984
- HEFFERNAN, ROY J., (WITH SULLIVAN, CHARLES L.), Convulsions following intravenous administration of pituitary extract, 675
- HELLENDALL, H., (WITH POLLARD, W. E.), Death due to intraperitoneal rupture of strictured lymphogranulomatous rectum during parturition, 317
- HERTIG, ARTHUR T., (WITH ROCK, JOHN), Some aspects of early human development, 973
- HOLDEN, FREDERICK C., Partial colpocleisis as approach to vesicovaginal fistula following total hysterectomy, 880
- HUGHES, WENDELL L., AND MARTIN, ARTHUR C., Treatment of hyperemesis gravidarum with intramuscular injections of husband's blood, 103
- HUNBLEY, J. MASON, JR., DIEHL, WILLIAM K., AND DIGGS, EVERETT S., Hormonal influences upon ureter, 858

## I

- ISENHOUR, C. E., (WITH ROBINSON, C. E., DILL, L. V., AND CADDEN, J. F.), Glomerular filtration and renal blood flow in hypertensive woman and in posttoxicemic hypertension, 616
- , (WITH DILL, L. V., CADDEN, J. F., AND ROBINSON, C. E.), Glomerular filtration and renal blood flow in "normal" patients following toxemias of pregnancy, 66
- ISRAEL, S. LEON, Clinical similarity of corpus luteum cyst and ectopic pregnancy, 22

- IVINS, JOSEPH L., (WITH EVANS, WILLIAM B., AND SICKEL, GEORGE B.), Primary ovarian pregnancy, 528
- IVY, A. C., Functional anatomy of labor, with special reference to human being, 952

## J

- JACOBY, ADOLPH, AND DERBRUCKE, MAURICE G., Vaginal iontophoresis of choline compound, 250
- JAVERT, CARL T., (WITH STEELE, KYLE B.), Classification of obstetric pelvis based on size, mensuration, and morphology, 783
- JOHNSON, C. GORDON, Use of mercurochrome to avoid postoperative catheterizations, 98

## K

- KANTROWITZ, A. R., (WITH FISCHER, HENRY S.), Sarcoma botryoides of cervix, 141
- KAUFMAN, J. D., (WITH LASH, A. F.), Unilateral twin ectopic pregnancy, 342
- KEYES, JOHN L., AND WHITEHOUSE, A. J., Portes cesarean section, 705
- KHARASCH, MORRIS S., (WITH DIECKMANN, WILLIAM J.), Solution of posterior pituitary sulfonate (pit-sulfonate) in labor, 820
- KIRSCHBAUM, HARRY M., Scopolamine in obstetrics, 664
- KLINGENSMITH, PAUL, Posterior rotation of occiput during labor, 623
- KOBAK, DISRAELI, (WITH FALLS, FREDERICK H., AND BERNELL, EDWARD C.), Conservative treatment of pelvic inflammation with Newman thermo-flo, 240
- KOSMAK, GEORGE W., A tribute to Hugo Ehrenfest, 369
- , Gynecologic and other implications which relate to an ageing female population, 897
- KREBS, JOSEPH M., Routine use of bicycle exercises for prophylaxis of postoperative thrombophlebitis, 73
- KRIEG, EARL G., Treatment of pelvic inflammatory disease with intradermal administration of bacillus coli vaccine, 681
- KROHN, LEON, HARRIS, JOSEPH, AND HECHTER, OSCAR, Sources of error in detection of ovulation, 213
- KULKA, E. W., True bone formation in Fallopian tube, 384
- KUSHNER, J. IRVING, (WITH WAHRSINGER, PHILIP B.), Elderly primigravida, 505
- , (WITH SMILEY, IRVING), Rare connective tissue tumor (myxosarcoma) in area of Bartholin gland, 709

## L

- LANGMAN, LOUIS, AND RUE, H. S., Electrometric timing of human ovulation, 223
- LASH, A. F., AND KAUFMAN, J. D., Unilateral twin ectopic pregnancy, 342
- LAUGHLIN, K. A., (WITH TRUSSELL, RAY E., WILSON, MAE L., AND LONGWELL, F. H.), Vaginal trichomoniasis, 292



- TUCKER, WILLIAM B., (WITH EISELE, C. WESLEY, VINES, ROBERT W., AND BATTY, JOHN L.), Problem of unsuspected tuberculosis in pregnancy, 183
- TURINO, T. R., (WITH DUCKMAN, S.), Use of methyl testosterone for relief of breast engorgement in puerperium, 112

## V

- VELKOFF, ABRAHAM, AND FERGUSON, A. DREW, Bilateral dry gangrene of both lower extremities due to ergot, 331
- VINES, ROBERT W., (WITH EISELE, C. WESLEY, TUCKER, WILLIAM B., AND BATTY, JOHN L.), Problem of unsuspected tuberculosis in pregnancy, 183
- VOGT, WILLIAM H., JR., AND HAMILTON, EUGENE G., Statistical study of 500 consecutive abdominal hysterectomies, 723

## W

- WAHRSINGER, PHILIP B., AND KUSHNER, J. IRVING, Elderly primigravida, 505
- WARD, GEORGE GRAY, Diagnosis and treatment of carcinoma of corpus uteri based on experiences at Women's Hospital, 303
- WATERS, EDWARD G., Selective hysterectomy for nonmalignant uterine disease, 1107
- , CARTWRIGHT, EAKLE W., AND LYNCH, J. EDWARD, Immediate postpartum repair of old perineal lacerations, 124

- WHITEHOUSE, A. J., (WITH KEYES, JOHN L.), Portes cesarean section, 705
- WHITTEMORE, W. STEWART, Pregnancy following operation for congenital absence of vagina, 516
- WILLIAMS, GEORGE A., Improved vehicle for medication of vagina, 153
- WILLIAMS, PHILIP F., AND FRALIN, FLOR-ENCE G., Nutrition study in pregnancy, 647
- WILLIS, RAYMOND S., WINN, WATT W., MORRIS, A. TRUETT, NEWSOM, A. A., AND MASSEY, WARREN E., Clinical observations in treatment of nausea and vomiting in pregnancy with vitamins B<sub>1</sub> and B<sub>6</sub>, 265
- WILSON, MARY E., (WITH TRUSSELL, RAY E., LONGWELL, F. H., AND LAUGHLIN, K. A.), Vaginal trichomoniasis, 292
- WINKELSTEIN, L. B., Prostigmine methyl-; sulfate and delayed menstruation, 231
- WINN, WATT W., (WITH WILLIS, RAYMOND S., MORRIS, A. TRUETT, NEWSOM, A. A., AND MASSEY, WARREN E.), Clinical observations in treatment of nausea and vomiting in pregnancy with vitamins B<sub>1</sub> and B<sub>6</sub>, 265
- WRORK, DONALD H., AND BRODERS, ALBERT C., Adenomyosis of Fallopian tube, 412

## Z

- ZONDEK, BERNHARD, AND SHAPIRO, BENYAMIN, Simplified method of glycogen estimation in uterine mucosa for clinical purposes, 345

- PULVER, MICHAEL, AND POSNER, LEWIS B., Colostrum test for pregnancy in prenatal clinic, 690
- PUND, EDGAR, (WITH TORPIN, RICHARD, AND PEEPLES, W. J.), Etiologic and pathologic factors in series of 1,741 fibromyomas of uterus, 569

## R

- REID, DUNCAN E., (WITH GIBBS, FREDERIC A.), Electroencephalogram in pregnancy, 672
- REYCRAFT, J. L., AND PLATZ, CHARLES P., Incidence of placenta previa during a ten-year period at Cleveland Maternity Hospital (1931-1940), 509
- REYNOLDS, SAMUEL R. M., Method for correlating data from menstrual cycles of different lengths, 151
- ROBINSON, C. E., (WITH DILL, L. V., ISENHOUR, C. E., AND CADDEN, J. F.), Glomerular filtration and renal blood flow in "normal" patients following toxemias of pregnancy, 66
- , DILL, L. V., CADDEN, J. F., AND ISENHOUR, C. E., Glomerular filtration and renal blood flow in hypertensive woman and in posttoxicemic hypertension, 616
- ROCK, JOHN, AND HERTIG, ARTHUR T., Some aspects of early human development, 973
- RUBIN, I. C., Progress in myomectomy, 196
- RUCKER, M. PIERCE, (WITH PRIDE, C. B.), Eclampsia and ovarian pregnancy, 575
- RUTHERFORD, ROBERT N., Changes in female genital tract during puerperium induced by sex hormone therapy, 595

## S

- SCHEFFEY, LEWIS C., Malignancy subsequent to irradiation of uterus for benign conditions, 925
- SCHERLIS, SIDNEY, AND SOLOWAY, LEWIS R., Pregnancy and labor in patient with cardiac anomaly, probable tetralogy of Fallot, 697
- SCHILLER, SARA, (WITH SMITH, GEORGE VAN S., AND SMITH, O. WATKINS), Clinical experiments in relation to excretion of estrogens, 455
- , (WITH SMITH, GEORGE VAN S., AND SMITH, O. WATKINS), Clinical experiments in relation to excretion of estrogens, 606
- SCOTT, ROGER B., (WITH EVERETT, HOUSTON S.), Possible etiologic role of gynecologic lesions in production of hypertension, 1010
- SHANDORF, JAMES F., (WITH DOUGLAS, R. GORDON, AND DAVIS, IONA F.), Gonorrhea in female and its treatment with sulfonamides, 1026
- SHAPIRO, BENYAMIN, (WITH ZONDEK, BERNHARD), Simplified method of glycogen estimation in uterine mucosa for clinical purposes, 345
- SHULMAN, ALEX, (WITH MARX, RUDOLPH, AND GLASS, SAMUEL), Experimentally produced fibroids in guinea pig and their possible analogy to myomas in human being, 259
- SHUTE, EVAN, Vitamin E and premature labor, 271

- SICKEL, GEORGE B., (WITH EVANS, WILLIAM E., AND IVINS, JOSEPH L.), Primary ovarian pregnancy, 528
- SILBERNAGEL, WYNNE M., AND FIDLER, ROSWELL S., Ante-partum rupture of umbilical vein, 712
- SMILEY, IRVING, AND KUSHNER, J. IRVING, Rare connective tissue tumor (myxosarcoma) in area of Bartholin gland, 709
- SMITH, GEORGE VAN S., SMITH, O. WATKINS, AND SCHILLER, SARA, Clinical experiments in relation to excretion of estrogens, 455, 606
- SMITH, O. WATKINS, (WITH SMITH, GEORGE VAN S., AND SCHILLER, SARA), Clinical experiments in relation to excretion of estrogens, 455, 606
- SNYDER, FRANKLIN F., Experimental production of toxemia of pregnancy, 1091
- SOLOWAY, LEWIS R., (WITH SCHERLIS, SIDNEY), Pregnancy and labor in patient with cardiac anomaly, probable tetralogy of Fallot, 697
- SOULE, S. D., Estrogen-withdrawal bleeding, 684
- STANDER, H. J., Treatment of bleeding in first and third trimesters of pregnancy, 531
- , Treatment of heart disease in pregnancy, 714
- STEELE, KYLE B., AND JAVERT, CARL T., Classification of obstetric pelvis based on size, mensuration, and morphology, 783
- STUDDIFORD, WILLIAM E., Primary peritoneal pregnancy, 487
- SULKOWITZ, HIRSH W., (WITH FINE-SINGER, JACOB E., AND MEIGS, JOE V.), Clinical, psychiatric and psychoanalytic study of case of male pseudohermaphroditism, 310
- SULLIVAN, CHARLES L., AND HEFFERNAN, ROY J., Convulsions following intravenous administration of pituitary extract, 675
- SWEET, LEWIS K., (WITH PARKS, JOHN), Does antenatal use of vitamin K prevent hemorrhage in newborn infant, 432

## T

- TAUSSIG, FRED J., In memoriam, Hugo Ehrenfest, 367
- TAYLOR, ROBERT, Review of Caldwell-Moley method of roentgen pelvic mensuration with correlation of new technical procedures, 348
- TILDEN, I. L., (WITH MILNOR, G. C.), Endometrial cyst of groin associated with decidual reaction in appendix, 324
- TOLAND, OWEN JONES, Hydatid mole with high persistent titer of gonadotropic hormone, 502
- TORPIN, RICHARD, (GREENBLATT, ROBERT B., AND MORTARA, FRANK), Sexual libido in female, 658
- , PUND, EDGAR, AND PEEPLES, W. J., Etiologic and pathologic factors in series of 1,741 fibromyomas of uterus, 569
- TRAUT, HERBERT F., Uses and abuses of radiation therapy in obstetrics and gynecology, 638
- TRUSSELL, RAY E., WILSON, MARY E., LONGWELL, F. H., AND LAUGHLIN, K. A., Vaginal trichomoniasis, 292

Brenner tumor, bibliography of, 180 (Correspondence)  
 bilateral, of ovary (Peale), 138  
 Brooklyn Gynecological Society, roster of, 181, 741

## C

Caldwell-Moloy method of roentgen pelvic mensuration with correlation of new technical procedures (Taylor), 348  
 Candidates certified by American Board of Obstetrics and Gynecology, 364  
 Capillary fragility in menometrorrhagia as and its changes following treatment with ascorbic acid (Pignoli), 547 (Abst.)  
 Carcinoma, cervical, previously treated with irradiation, (Scheffey), 926  
 corpus, extension of (Philipp and Huber), 172 (Abst.)  
 of corpus uteri, diagnosis and treatment of, at Woman's Hospital (Ward), 303  
 ovarian, bilateral, associated with intrauterine pregnancy (Bossert), 336  
 uterine, irradiation treatment of, intestinal injuries resulting from (Aldridge), 833  
 Cardiac failure, onset of, in women with rheumatic heart disease, pulse and respiratory rates during labor as guide to (Mendelson and Pardee), 370  
 Catheterization, postoperative, use of mercurochrome to avoid (Johnson), 98  
 Celomic walls, mesenchyme of, origin of endometriosis from (Gruenwald), 470  
 Central Association of Obstetricians and Gynecologists, item of, 924  
 roster of, 181, 741  
 Cephalic diameters (Moloy), 765  
 Cervix, sarcoma botryoides of (Fischer and Kantrowitz), 141  
 uteri, electrical study of (Langman and Burr), 544 (Abst.)  
 Cesarean section, anesthesia for, local, detailed technique of modified (Beck), 558  
 experience of Johns Hopkins Hospital with (Manahan, Connally, Jr., and Eastman), 999  
 Portes (Keyes and Whitehouse), 705  
 Chiari and Frommel's disease, persistent lactation with note on (Gilber), 359 (Abst.)  
 Chicago Gynecological Society, roster of, 181, 741  
 transactions of, 171  
 Childbirth mortality (Yerushalmy, Gardiner, and Palmer), 291 (Abst.)  
 Cholesterol ester and phospholipid determinations (Brewer), 1056  
 Choline compound, vaginal iontophoresis of (Jacoby and DerBrucke), 250  
 Chorionepithelioma (Dockerty and Craig), 497  
 Chorionic villi implants, benign multiple, in peritoneal cavity accompanied by hemoperitoneum (Lazarus and Schiffrin), 541 (Abst.)  
 Cincinnati Obstetrical Society, roster of, 181, 741  
 Cleveland Maternity Hospital, incidence of placenta previa during ten-year period at (Reycraft and Platz), 509  
 Colon, endometrioma, causing stricture (Blakley), 179 (Abst.)  
 Colostrum test for pregnancy in prenatal clinic (Pulver and Posner), 690  
 Colpocleisis, partial, as approach to vesicovaginal fistula following total hysterectomy (Holden), 880

Congenital absence of vagina, pregnancy following operation for (Whittemore), 516  
 aplasia, partial, of vagina (Dannreuther), 1063  
 Contractions, uterine, kymograph records of, 355 (Correspondence)  
 puerperal (Bickers), 581  
 wave of, in labor (Ivy), 952  
 Convulsions following intravenous administration of pituitary extract (Sullivan and Heffernan), 675  
 Corpus luteum cyst, clinical similarity of, and ectopic pregnancy (Israel), 22  
 differential diagnosis of, and tubal abortion (Israel), 24  
 excretion of pregnanediol and (Cope), 912 (Abst.)  
 human, studies of (Brewer), 1048  
 of pregnancy; clinical experiments on pregnancy maintaining effect of corpus luteum hormone after loss of (Ehrhardt), 917 (Abst.)  
 vascularity of (Brewer), 1049  
 uteri, carcinoma of, diagnosis and treatment of, at Women's Hospital (Ward), 303  
 Correspondence, 180, 355, 730, 920  
 Cortical hormone, prevention of experimental fibroids by (Lipschutz and Vargas), 913 (Abst.)  
 Cortilactin (Spor, Hartman, and Brownell), 360 (Abst.)  
 Curettage material, transplantation of, menstruation following, in endometrium-free uterus (Siebke), 550 (Abst.)  
 Cyst, corpus luteum, clinical similarity of, and ectopic pregnancy (Israel), 22  
 dermoid, ovarian, bilateral, complicating pregnancy treated by bilateral oophorectomy (Goodwin), 525  
 endometrial, of groin associated with decidual reaction in appendix (Milnor and Tilden), 324  
 pedunculated, of uterus (Levi), 178 (Abst.)

## D

Denver Obstetrical and Gynecological Society, roster of, 182, 742  
 Dermoid cysts, ovarian, bilateral, complicating pregnancy treated by bilateral oophorectomy (Goodwin), 525  
 Dihydrostilbestrol, estrogenic properties of (Bieren and Compton), 287  
 Dysenteriae, Flexner, urinary infection in pregnancy due to (Diddle and McKee), 481  
 Dysmenorrhea, essential, stilbestrol in relief of (Sturgis), 549 (Abst.)

## E

Eclampsia and ovarian pregnancy (Pride and Rucker), 575  
 Ectopic pregnancy, clinical similarity of corpus luteum cyst and (Israel), 22  
 twin, unilateral (Lash and Kaufman), 342  
 Editorial, women in war effort, 732  
 Ehrenfest, Hugo, in memoriam, 367  
 Electroencephalogram in pregnancy (Gibbs and Reid), 672  
 variations in, during menstrual cycle (de Barenne and Gibbs), 687  
 Electrolyte therapy of premenstrual distress (Greenhill and Freed), 548 (Abst.)  
 Electrometric timing of human ovulation (Langman and Burr), 223

# SUBJECT INDEX\*

## A

- Abdominal hysterectomies, statistical study of 500 consecutive, (Vogt, Jr., and Hamilton), 723
- Abortion, spontaneous, and its treatment with progesterone (Mason), 630
- tubal, differential diagnosis of corpus luteum cyst and (Israel), 24
- Abstracts, endocrinology, 911
- endometriosis, 172
- miscellaneous, 102, 133, 144, 146, 152, 212, 230, 291, 330, 350, 354, 383, 486, 491, 530, 541, 543, 605
- mammary glands, 357
- menstruation, 544
- myoma, 179
- placenta, 735
- Adenoacanthoma with ovarian metastases (Beecham and Friday), 512
- Adenomyosis of Fallopian tube (Wrook and Broders), 412
- Adolescence, menstrual abnormalities of (Sevringshaus), 545 (Abst.)
- Adrenal, lactation factor of (Spoor, Hartman, and Brownell), 360 (Abst.)
- Ageing female population, gynecologic and other implications which relate to an (Kosmak), 897
- Alabama Association of Obstetricians and Gynecologists, roster of, 182, 742
- Allergic shock caused by synapoidin (Phillips), 706
- Amenorrhea, treatment of, by means of intraovarian injections of hormone preparations (Stanca), 549 (Abst.)
- placental blood in (Halbrecht), 549 (Abst.)
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons, roster of, 181, 741
- Board of Obstetrics and Gynecology, candidates certified by, 364
- items of, 363, 552, 740, 923, 1118
- College of Surgeons, item of, 924, 1118
- Gynecological Society, papers of, 743-910, 925-1117
- roster of, 181, 741
- Medical Association, Section on Obstetrics and Gynecology, roster of, 181, 741
- obstetrical and gynecological societies, roster of, 181, 182, 741, 742
- Analgesic drugs (Mengert), 889
- obstetric, morphine sulfate as (Mengert), 888
- Androgen pellets, effects of (Greenblatt, Mortara, and Torpin), 661
- Anemia, macrocytic hyperchromic, of pregnancy (Daniel and Antis), 93
- Anencephalus diagnosed by x-ray (Payne and Bland), 593
- Anesthesia, local, modified, for cesarean section, detailed technique of (Beck), 558
- Anesthetic drugs (Mengert), 889
- Announcement, registry of ovarian tumors, 551, 922
- Antenatal use of vitamin K, does, prevent hemorrhage in newborn infant (Parks and Sweet), 432
- Aplasia, partial congenital, of vagina (Dannreuther), 1063
- Apoplexy, uteroplacental, methods of treating (Rauramo and Kahanpaa), 735 (Abst.)

- Appendix, decidual reaction in, endometrial cyst of groin associated with (Milnor and Tilden), 324
- Arthralgia, menopausal (Ishmael), 605 (Abst.)
- Artificial pyrexia in pregnant women (Mengert and Paul), 702
- Ascorbic acid, capillary fragility in menometrorrhagias and its changes following treatment with (Pignoli), 547 (Abst.)

## B

- Bacillus coli vaccine, intradermal administration of, treatment of pelvic inflammatory disease (Krieg), 681
- Baltimore Obstetrical and Gynecological Society, roster of, 181, 741
- Bartholin gland, myxosarcoma in area of (Smiley and Kushner), 709
- Benign conditions, irradiation of uterus for, malignancy subsequent to (Scheffey), 925
- Bicycle exercises for prophylaxis of postoperative thrombophlebitis, routine use of (Krebs), 73
- Bleeding, estrogen-withdrawal (Soule), 684
- in first and third trimesters of pregnancy, treatment of (Stander), 531
- juvenile, subsequent fate of girls with (Klingelhöfer), 546 (Abst.)
- uterine, functional, effect of progesterone in adolescent girls and young women with (Allen and Heckel), 984
- pathology of, in climacterium and postclimacterium (Pallos and Treite), 547 (Abst.)
- Blood flow, renal, and glomerular filtration in "normal" patients following toxemias of pregnancy (Dill, Isenhour, Cadden, and Robinson), 66
- husband's, intramuscular injections of, treatment of hyperemesis gravidarum with (Hughes and Martin), 103
- menstruation, coagulation defect in (Lozner, Taylor, and Taylor), 544 (Abst.)
- picture in Gujarati Hindu women (Mehta, Shah, and Jhaveri), 383 (Abst.)
- placental, in treatment of amenorrhea (Halbrecht), 549 (Abst.)
- pressure and sex hormones (Guirdham), 914 (Abst.)
- renal, flow and glomerular filtration in hypertensive woman and in posttoxicemic hypertension (Robinson, Dill, Cadden, and Isenhour), 616
- transfusion reaction due to intra-group incompatibility (Crooks), 121
- Bone formation, true, in Fallopian tube (Kulka), 384
- Books received, 742, 924
- Breast engorgement in puerperium, methyl testosterone for relief of (Duckman and Turino), 112
- lactating, anatomy of (Engel), 357 (Abst.)
- malignant lesions of (Marques), 146 (Abst.)

\*July, pp. 1-182; August, pp. 183-366; September, 367-552; October, pp. 553-742; November, pp. 743-924; December, pp. 925-1134.

- Glomerular filtration and renal blood flow in hypertensive woman and in posttoxemic hypertension (Robinson, Dill, Cadden, and Isenhour), 616  
 in "normal" patients following toxemias of pregnancy (Dill, Isenhour, Cadden, and Robinson), 66
- Glycogen estimation, method of, in uterine mucosa for clinical purposes (Zondek and Shapiro), 345
- Gonadotropic hormone, high persistent titer of, hydatid mole with (Toland), 502
- Gonorrhea in female and its treatment with sulfonamides (Douglas, Davis, and Shandorf), 1026
- Granulosa cell tumor, unusual coexistence of, and ovarian teratoma containing thyroid tissue (Murray, Dockerty, and Pemberton), 134
- lutein cells (Brewer), 1051
- Groin, endometrial cyst of, associated with decidual reaction in appendix (Milnor and Tilden), 324
- Gynecologic and other implications which relate to an ageing female population (Kosmak), 897
- hemorrhages, benign (Ward), 543 (Abst.)
- lesions in production of hypertension, possible etiologic role of (Everett and Scott), 1010
- operations, use of sulfanilamide powder in (Bibb), 464
- thought, contributions of studies on primate animals to (Hartman), 156
- Gynecology and obstetrics, influence of French school in sixteenth, seventeenth, and eighteenth centuries upon development of (Danforth), 743
- practical problems in, department of, 714
- pregnenediol determinations in (Hamblen, Cuyler, and Baptist), 442
- radiation therapy in, uses and abuses of (Traut), 638
- Gynecopathies, various, evidence of persistence of uteroovarian cycle in (Sammartino and Herrera), 544 (Abst.)

## H

- Head molding during labor, studies on (Moloy), 762
- Heart disease in pregnancy, treatment of (Stander), 714
- Heart disease, rheumatic, pulse and respiratory rates during labor as guide to onset of cardiac failure in women with (Mendelson and Pardee), 370
- Hemorrhage, gynecologic, benign (Ward), 543 (Abst.)
- in newborn infant, does antenatal use of vitamin K prevent? (Parks and Sweet), 432
- in puberty, therapy of (Vöge), 546 (Abst.)
- puerperal, severe late, placental polyp with (Dorsey), 591
- uterine functional, treatment of, by male hormone (Bompard), 916 (Abst.)
- Hexestrol, estrogenic properties of (Bieren and Compton), 287
- Hormonal content of parovarian cystic fluid removed during pregnancy (Pardini), 919 (Abst.)
- influences upon ureter (Hundley, Jr., Diehl, and Diggs), 858
- Hormone, corpus luteum, clinical experiments on pregnancy maintaining effect of, after loss of corpus luteum of pregnancy (Ehrhardt), 917 (Abst.)

## Hormone—Cont'd

- cortical, prevention of experimental fibroids by (Lipschutz and Vargas), 913 (Abst.)
- female sex, use of, in disorders of women (Smith), 911 (Abst.)
- follicle, effect of, on function of human uterine musculature (Kneer), 913 (Abst.)
- on uterine activity (Slevers and Schenz), 918 (Abst.)
- influence of, on bladder capacity (Hoffmann and Treite), 914 (Abst.)
- follicle-stimulating, of anterior pituitary in menstrual disorders, intravenous use of (Kenny), 548 (Abst.)
- gonadotropic, high persistent titer of, hydatid mole with (Toland), 502
- lactogenic, prolactin as (Folley and Young), 358 (Abst.)
- male, treatment of uterine functional hemorrhages by (Bompard), 916 (Abst.)
- preparations, intra-ovarian injections of, late results in treatment of amenorrhea by means of (Stanca), 549 (Abst.)
- sex, and blood pressure (Guirdham), 914 (Abst.)
- female, current status of (Hoskins), 915 (Abst.)
- male, influence of, on female breast (Preisseecker), 360 (Abst.)
- therapy and opotherapy in menopause (Hoepfner), 915 (Abst.)
- sex, changes in female genital tract during puerperium induced by (Rutherford), 595
- Human development, early, some aspects of (Rock and Hertig), 973
- Hydatid mole with high persistent titer of gonadotropic hormone (Toland), 502
- Hydramnios, acute, with anencephalus diagnosed by x-ray (Payne and Bland), 593
- Hyperemesis gravidarum, treatment of, with intramuscular injections of husband's blood (Hughes and Martin), 103
- Hypertension, posttoxemic, glomerular infiltration and renal blood flow in hypertensive woman and in (Robinson, Dill, Cadden, and Isenhour), 616
- production of, possible etiologic role of gynecologic lesions in (Everett and Scott), 1010
- Hysterectomies, abdominal, statistical study of 500 consecutive (Vogt, Jr., and Hamilton), 723
- Hysterectomy, selective, for nonmalignant uterine disease (Waters), 1107
- total, vesicovaginal fistula following, partial colpocleisis as approach to (Holden), 880

## I

- Impetigo contagiosa, bacteriology of (Cruikshank), 133 (Abst.)
- In memoriam, Hugo Ehrenfest, 367
- Incontinence, urinary stress, transplantation of fascia for relief of (Alldridge), 398
- Infant, newborn, hemorrhage in, does antenatal use of vitamin K prevent? (Parks and Sweet), 432
- infection of, with vaginal trichomoniasis (Trussell, Wilson, Longwell, and Laughlin), 292
- resuscitation of, apparatus for (Biskind and Eichner), 147; (Alexander and Martin), 351
- toxic manifestations in, following placental transmission of sulfanilamide (Ginzler and Chesner), 46
- prematurely born, mortality of (Diddle and Plass), 279

- Endocrine factors involved in development and function of mammary gland (Fredrikson), 357 (Abst.)  
 influences on lactation (Antoine), 362 (Abst.)  
 therapy of ovarian failure (Hamblen and Pullen), 918 (Abst.)  
 Endocrinology, 911 (Absts.)  
 Endometrial cyst of groin associated with decidual reaction in appendix (Milnor and Tilden), 324  
 pedunculated, of uterus (Levi), 178 (Abst.)  
 Endometrioma of colon causing stricture (Blaikley), 179 (Abst.)  
 rectal (Bazy, Blondin, and Chene), 178 (Abst.)  
 Endometriosis, 172 (Absts.)  
 and ascites, fibroma ovarii with (Tasch), 179 (Abst.)  
 and pregnancy (Portes and Varangot), 178 (Abst.)  
 clinical features of (Philipp and Huber), 172 (Abst.)  
 externa, clinic on (Turunen), 176 (Abst.)  
 of cervical origin (von Torzsay-Kiss), 177 (Abst.)  
 origin of (Philipp and Huber), 172 (Abst.)  
 from mesenchyme of celomic walls (Gruenwald), 470  
 pathogenesis of (Philipp and Huber), 175 (Abst.)  
 postmenopausal (Frank and Geist), 652  
 scar (Wespi and Kletzhandler), 177 (Abst.)  
 significance of (Meigs), 176 (Abst.)  
 tubal, incidence of (Rintelen), 176 (Abst.)  
 Endometrium, atypical histopathologic diagnoses of (Mann, Meranze, and Golub), 460  
 Enemas, improperly administered, injury to rectum from (Ballon and Goldbloom), 212  
 Ergot as cause of bilateral dry gangrene of both lower extremities (Velkoff and Ferguson), 331  
 Erythroblastosis fetalis, vitamin C deficiency as possible factor in pathogenesis of (Burnham), 920 (Correspondence)  
 Estradiol benzoate and progesterone, cyclic administration of, urinary estrogens before, during, and after (Smith, Smith, and Schiller), 606  
 effect of, on contractions (Bickers), 583  
 Estriol, urinary estrogens before, during and after (Smith, Smith, and Schiller), 606  
 Estrogen induced mammary tumors, regression of, in female rats (Noble and Collip), 362 (Abst.)  
 therapy, cyclical (Palmer), 56  
 in menopause, methods for objective evaluation of (Bennett, Jr.), 296  
 treatment in female eunuchoid (Goldzieher and Adler), 491 (Abst.)  
 Estrogen-withdrawal bleeding (Soule), 684  
 Estrogenic properties of dihydrostilbestrol (hexestrol) (Bieren and Comp-ton), 287  
 Estrogenic treatment of menopausal symptoms and senile vaginitis, correlation of vaginal smear changes in (Ottoway), 915 (Abst.)  
 Estrogens, effects of, on lactation (Folley), 361 (Abst.)  
 excretion of, clinical experiments in relation to (Smith, Smith, and Schiller), 455, 606  
 in treatment of leucoplakia, kraurosis, and senile vaginitis, use of (Buxton), 109  
 Estrogens—Cont'd  
 synthetic, use and potency of (Greenhill), 475  
 urinary, before and after injection of estrone into patient with surgical menopause (Smith, Smith, and Schiller), 455, 606  
 Estrone, injection of, urinary estrogens before and after, into patient with surgical menopause (Smith, Smith, and Schiller), 455  
 Eunuchoid, female, estrogen treatment in (Goldzieher and Adler), 491 (Abst.)  
 Excretion of estrogens, clinical experiments in relation to (Smith, Smith, and Schiller), 455, 606  
 F  
 Fallopian tube, adenomyosis of (Wrook and Broders), 412  
 bone formation in, true (Kulka), 384  
 Family living, core of creative—prepared parents (Corbin), 166  
 Fascia, transplantation of, the relief of urinary stress incontinence (Aldridge), 398  
 Female sex hormone, current status of (Hoskins), 915 (Abst.)  
 Fetal and neonatal mortality, causes of (D'Esopo and Marchetti), 1  
 squamas, identification of, and diagnosis of ruptured membranes by vaginal smear (Bourgeois), 80  
 Fibroid tumors, similar, occurring in identical twins (Grosbeck and Pool), 179 (Abst.)  
 Fibroids, experimental, prevention of, by cortical hormone (Lipschutz and Vargas), 913 (Abst.)  
 experimentally produced, in guinea pig and their possible analogy to myomas in human being (Marx, Glass, and Shulman), 259  
 Fibroma of ovary (Brody), 521  
 ovarii with endometriosis and ascites, (Tasch), 179 (Abst.)  
 Fibromyomas of uterus, etiologic and pathologic factors in series of 1,741 (Torpin, Pund, and Peebles), 569  
 Fistula, vesicovaginal, following total hysterectomy, partial colpocleisis as approach to (Holden), 880  
 surgical treatment and postoperative care of (Miller), 873  
 Flexner dysenteriae, urinary infection in pregnancy due to (Diddle and McKee), 481  
 Follicle hormone, effect of, on function of human uterine musculature (Kneer), 913 (Abst.)  
 on uterine activity (Sievers and Schenz), 918 (Abst.)  
 influence of, on bladder capacity (Hoffmann and Treite), 914 (Abst.)  
 Forceps, Willett's, danger of, in placenta previa (Browne), 740 (Abst.)  
 Fragility, capillary, in menometrorrhagias and its changes following treatment with ascorbic acid (Pignoli), 547 (Abst.)  
 Friedman-Brouha reaction, diagnosis of pregnancy by, aided by transperitoneal ovarioscopy (Crainicianu), 738 (Abst.)  
 G  
 Gangrene, bilateral dry, of both lower extremities due to ergot (Belkoff and Ferguson), 331  
 Genital tract, female, changes in, during puerperium induced by sex hormone therapy (Rutherford), 595  
 Glands, mammary, 357 (Absts.)

In the two cases marked poor, one (E. A.<sup>1</sup>) should really be eliminated because in this patient methyl testosterone was not started until the sixth day and the patient's breasts were pumped twice daily from the second to the fifth day post partum. It has been shown that once suckling has begun, there is a reflex stimulation for further milk production, hence in this case too much was expected of the methyl testosterone.

In P.,<sup>1</sup> the second of the "poor" results, the breasts responded fairly well to the 150 mg. dose, but on the following day they filled in again.

Of the four cases designated as fair, additional information is offered. In one case (S.<sup>1</sup>), there was moderate hirsutism which was mentioned before. In another (M. G.), a very small dose was used, this being one of the early cases. If a larger dose had been employed, the results might have been more favorable, although this is conjectural.

The third case (R. B.), para ii, nursed her baby on the third day, bringing in another factor previously mentioned.

The fourth case (H. S.) was a gravida v, para ii, who had three abortions, 1 spontaneous and the other 2 induced. She was a very thin, nervous woman weighing ninety pounds when first seen in pregnancy at the fifth month. Because of her malnutrition and extreme nervousness, a basal metabolic rate test was attempted on two occasions without success; she did not cooperate well. Her infant died on the third day post partum quite suddenly. From her very make-up, there appears to have been a thyroid dyscrasia.

Since it is believed that the uteri of nursing mothers involute better than those that do not nurse, the fundus was watched particularly for subinvolution. It was noted in only three cases, or 6 per cent, of the series. Therefore, it is believed that this is negligible, since a similar number of subinvolved uteri is seen in nursing mothers.

As far as dosage is concerned, it varied from a minimum of 60 mg. to 270 mg. (one case). The dose most commonly employed by us is 150 mg. divided into 5 doses every four hours. This is approximately equivalent to 50 mg. of parenteral testosterone propionate.

The age of the patients varied from twenty to forty, and in both of these extremes the results were good, with the exception of the one case (R. B.) previously discussed. Therefore, age would seem to have no influence on the results.

Gravidity and parity also seemed to have little effect on the influence of the medication.

The type of delivery too played no role whatsoever, although this series is too small to prove this point conclusively.

#### CONCLUSION

Methyl testosterone orally supplies a very effective means of relieving breast engorgement in the puerperium. The method suggested is 150 mg. in 5 doses of 30 mg. each, every four hours, beginning on the third or fourth day post partum when the breasts are full.

#### SUMMARY

1. A study of a series of 50 cases is presented, showing the effect of oral methyl testosterone on the inhibition of lactation.
2. A suggestion as to the method of use is offered.

- Infection, urinary, in pregnancy due to Flexner dysenteriae (Diddle and McKee), 481
- Inflammation, pelvic, conservative treatment of, with Newman thermoflo (Falls, Bernell, and Kobak), 240
- Injuries, intestinal, resulting from irradiation treatment of uterine carcinoma (Aldridge), 833
- Intersexuality, factors affecting (Quintela), 913 (Abst.)
- Intestinal injuries resulting from irradiation treatment of uterine carcinoma (Aldridge), 833
- Intrauterine pregnancy, bilateral ovarian carcinoma associated with (Bossert), 336
- Intravenous drip and other intensive methods for treatment of early syphilis (Eagle and Hogan), 486 (Abst.)
- Intubation, uterine (Bunster), 350 (Abst.)
- Irradiation of uterus for benign conditions, malignancy subsequent to (Scheffey), 925
- treatment of uterine carcinoma, intestinal injuries resulting from (Aldridge), 833
- Iodine therapy and thyroid extract in pregnancy toxemia, 730 (Correspondence)
- Iontophoresis, vaginal, of choline compound (Jacoby and DerBrucke), 250
- Item, American Board of Obstetrics and Gynecology, 363, 552, 740, 923, 1118
- American College of Surgeons, 924, 1118
- Central Association of Obstetricians and Gynecologists, 924

## J

- Johns Hopkins Hospital, experience of, with cesarean section (Manahan, Connally, Jr., and Eastman), 999

## K

- Kraurosis, estrogens in treatment of (Buxton), 109
- Kymograph records of uterine contractions, 355 (Correspondence)

## L

- Labor, functional anatomy of (Ivy), 952
- head molding during, studies on (Moloy), 762
- occiput during, posterior rotation of (Klingensmith), 623
- pit-sulfonate in (Dieckmann and Kharasch), 820
- posterior pituitary sulfonate in, solution of (Dieckmann and Kharasch), 820
- pregnancy and, in patient with cardiac anomaly, probable tetralogy of Fallot (Scherlis and Soloway), 697
- premature, vitamin E and (Shute), 271
- pulse and respiratory rates during, as guide to onset of cardiac failure in women with rheumatic heart disease (Mendelson and Pardee), 370
- uterine tonus during (Murphy), 694
- Lacerations, perineal, immediate postpartum repair of old (Waters, Cartwright, and Lynch), 124
- Lactation (Fauvet), 358 (Abst.)
- during puerperium, new means of increasing (Lehmann), 358 (Abst.)
- effects of estrogens on (Folley), 361 (Abst.)

## Lactation—Cont'd

- endocrine influences on (Antoine), 362 (Abst.)
- factor of adrenal (Spoor, Hartman, and Brownell), 360 (Abst.)
- inhibition of (Fleischer and Kushner), 361 (Abst.)
- persistent (Gilber), 359 (Abst.)
- prolonged, tetany following, on deficient diet (Anderson and Brown), 360 (Abst.)
- suppression of, by testosterone (Duffy and Corsaro), 361 (Abst.)
- Lesions, gynecologic, possible etiologic role of, in production of hypertension (Everett and Scott), 1010
- malignant, of breast (Marques), 146 (Abst.)
- Leucoplakia, estrogens in treatment of (Buxton), 109
- Louisville Obstetrical and Gynecological Society, roster of, 181, 741
- Lymphogranuloma venereum (Patterson), 144 (Abst.)
- Lymphogranulomatous rectum, stricture of, death due to intraperitoneal rupture of, during parturition (Pollard and Hellendall), 317

## M

- Male pseudohermaphroditism, clinical, psychiatric and psychoanalytic study of (Finesinger, Meigs, and Sulkowitch), 310
- Malignancy subsequent to irradiation of uterus for benign conditions (Scheffey), 925
- Mammary carcinoma, response to implantation of male hormone and progesterone (Loeser), 152 (Abst.)
- glands, 357 (Absts.)
- development and function of, endocrine factors involved in (Fredrickson), 357 (Abst.)
- pain and secretion, treatment of, with testosterone propionate (Nathanson, Meigs, and Parsons), 360 (Abst.)
- tumors, estrogen induced, regression of, in female rats (Noble and Collip), 362 (Abst.)
- Mastitis, chronic, testosterone in, local injunction of (Spence), 361 (Abst.)
- puerperal, early, roentgen ray treatment of (Wirth and Peters), 362 (Abst.)
- Maternal welfare, observations on (Jackson), 230 (Abst.)
- Menopausal arthralgia (Ishmael), 605 (Abst.)
- symptoms and senile vaginitis, correlation of vaginal smear, changes in estrogenic treatment of (Ottoway), 915 (Abst.)
- Menopause, estrogen therapy in, methods for objective evaluation of (Bennett, Jr.), 296
- opotherapy and hormone therapy in (Hoepfner), 915 (Abst.)
- surgical correction of, by ovarian isoplastism (Bennett and Russell, Jr.), 550 (Abst.)
- urinary estrogens before and after injection of estrone into patient with (Smith, Smith, and Schiller), 455
- Menorrhagia, surgical correction of, by ovarian isoplastism (Bennett and Russell, Jr.), 550 (Abst.)
- Menstrual abnormalities of adolescence (Sevringhaus), 545 (Abst.)
- blood, coagulation defect in (Lozner, Taylor, and Taylor), 544 (Abst.)



## Menstrual—Cont'd

- cycle (Hartman), 157
- method for correlating data from, of different lengths (Reynolds), 151
- variations in electroencephalogram during (de Barenne and Gibbs), 687
- disorders, follicle-stimulating hormone of anterior pituitary in, intravenous use of (Kenney), 548 (Abst.)
- Menstruation, 544 (Absts.)
- corpus luteum of, evidence for early onset of regression of (Brewer), 1048
- delayed, prostigmine methylsulfate and (Winkelstein), 231
- treatment of, with prostigmine (Grossmann), 549 (Abst.)
- first, relationship between, and clinical onset of tuberculosis (Nobecourt), 545 (Abst.)
- following transplantation of curettage material in endometrium-free uterus (Siebke), 550 (Abst.)
- influence of, on suspension stability of red cells (Greene), 544 (Abst.)
- Mercurochrome, use of, to avoid post-operative catheterizations (Johnson), 98
- Mesenchyme of celomic walls, origin of endometriosis from (Gruenwald), 470
- Metabolism and nutrition (Kosmak), 902
- Metastases, ovarian, adenocarcinoma with (Beecham and Friday), 512
- Methyl testosterone for relief of breast engorgement in puerperium (Duckman and Turino), 112
- Michigan Society of Obstetricians and Gynecologists, roster of, 182, 742
- Milk, secretion of, effect of visible light upon (Menju), 359 (Abst.)
- Morphine sulfate as obstetric analgesic (Mengert), 888
- Mortality, childbirth (Yerushalmy, Gardiner, and Palmer), 291 (Abst.)
- fetal and neonatal, causes of (D'Esopo and Marchetti), 1
- of prematurely born infants (Diddle and Plass), 279
- Mucosa, uterine, glycogen estimation in, method of, for clinical purposes (Zondek and Shapiro), 345
- Myomas (Huber), 172, 179 (Absts.)
- malignant (Hussy), 180 (Abst.)
- possible analogy to experimentally produced fibroids in guinea pig and their (Marx, Glass, and Shulman), 259
- Myometrectomy (Cirio), 180 (Abst.)
- Myomectomy, progress in (Rubin), 196
- Myxosarcoma in area of Bartholin gland (Smiley and Kushner), 709

## N

- Nausea and vomiting in pregnancy, clinical observations in treatment of, with vitamin B<sub>1</sub> and B<sub>6</sub> (Willis, Winn, Morris, Newsom, and Massey), 265
- New England Obstetrical and Gynecological Society, roster of, 181, 741
- New Orleans Obstetrical and Gynecological Society, roster of, 182, 742
- New York Obstetrical Society, roster of, 181, 741
- transactions of, 542
- Newborn infant, hemorrhage in, does antenatal use of vitamin K prevent? (Parks and Sweet), 432
- infants, resuscitation of, apparatus for (Biskind and Eichner), 147; (Alexander and Martin), 351

- Newman thermo-flo, conservative treatment of pelvic inflammation with (Falls, Bernell, and Kobak), 240
- Nursing, physiology of, contribution to (Feldweg), 357 (Abst.)
- under conditions of thirst or excessive ingestion of fluids (Olsen), 359 (Abst.)
- Nutrition and metabolism (Kosmak), 902
- study in pregnancy (Williams and Fralin), 647

## O

- Obstetric analgesic, morphine sulfate as (Mengert), 888
- operations, use of sulfanilamide powder in (Bibb), 464
- pelvis, classification of, based on size, mensuration, and morphology (Steele and Javert), 783
- Society of Syracuse Hospitals, roster of, 182, 742
- Obstetrical Society of Boston, roster of, 181, 741
- transactions of, 542
- of Philadelphia, roster of, 181, 741
- transactions of, 542
- Obstetrics and gynecology, influence of French school in sixteenth, seventeenth, and eighteenth centuries upon development of (Danforth), 743
- practical problems in, department of, 714
- pregnenediol determinations in (Hambelen, Cuyler, and Baptist), 442
- radiation therapy in, uses and abuses of (Traut), 638
- scopolamine in (Kirschbaum), 664
- utopian (Bartholomew), 553
- Occiput, posterior rotation of, during labor (Klingensmith), 623
- Oligomenorrhea, surgical correction of, by ovarian isoplastism (Bennett and Russell, Jr.), 550 (Abst.)
- Oophorectomy, bilateral, ovarian dermoid cysts complicating pregnancy treated by (Goodwin), 525
- Operation for congenital absence of vagina, pregnancy following (Whittemore), 516
- Operations, gynecologic and obstetric, use of sulfanilamide powder in (Bibb), 464
- Opotherapy and hormone therapy in menopause (Hoepfner), 915 (Abst.)
- Ova, abnormal, frequency of (Rock and Hertig), 981
- Ovarian carcinoma, bilateral, associated with intrauterine pregnancy, (Bossert), 336
- dermoid cysts, bilateral, complicating pregnancy treated by bilateral oophorectomy (Goodwin), 525
- failure, endocrine therapy of (Hambelen and Pullen), 918 (Abst.)
- function, vaginal smears correlated to (Bennett and Russell), 919 (Abst.)
- isoplastism, surgical correction of oligomenorrhea, menorrhagia and menopause by (Bennett and Russell, Jr.), 550 (Abst.)
- metastases, adenocarcinoma (Beecham and Friday), 512
- pregnancy and eclampsia (Pride and Rucker), 575
- primary (Evans, Sickel, and Ivins), 528
- ruptured (Courtiss), 128
- teratoma, unusual coexistence of granulosa cell tumor and, containing thyroid tissue (Murray, Dockerty, and Pemberton), 134
- tumors, registry of, 551, 922

- Ovarioscopy, transperitoneal, diagnosis of pregnancy by Friedman-Brown reaction, aided by (Crainicianu, 738 (Abst.))
- Ovary, Brenner tumor of, bilateral (Peale), 138
- fibroma of (Brody), 521
- Ovulation, detection of, sources of error in (Krohn, Harris, and Hechter), 213
- human, electrometric timing of (Langman and Burr), 223
- probable time of (Rock and Hertig), 974
- Oxytocics in puerperium (Bickers), 583
- P
- Pacific Coast Obstetrical and Gynecological Society, roster of, 182, 742
- Parents, prepared—core of creative family living (Corbin), 166
- Parovarian cystic fluid, hormonal content of, removed during pregnancy (Pardini), 919 (Abst.)
- Pelvic classification (Dickinson and Procter), 585
- conformation, observations of development of (Morton), 799
- inflammation, treatment of, conservative, with Newman thermo-flo (Falls, Bernell, and Kobak), 240
- inflammatory disease, treatment of, with intradermal administration of bacillus coli vaccine (Krieg), 681
- menstruation, roentgen, Caldwell-Moloy method of, with correlation of new technical procedures (Taylor), 348
- Pelvis, female, comparative measurements of (Dickinson and Procter), 585
- obstetric, classification of, based on size, mensuration, and morphology (Steele and Javert), 783
- Perineal lacerations, immediate postpartum repair of old (Waters, Cartwright, and Lynch), 124
- Peritoneal pregnancy, primary (Studdiford), 487
- Phospholipid and cholesterol ester determinations (Brewer), 1056
- Pit-sulfonate in labor (Dieckmann and Kharasch), 820
- Pittsburgh Obstetrical and Gynecological Society, roster of, 181, 741
- transactions of, 171, 543
- Pituitary extract, convulsions following intravenous administration of (Sullivan and Heffernan), 675
- posterior, reactivity to, during pregnancy, relation between uterine activity and (Murphy), 117
- sulfonate, posterior, solution of, in labor (Dieckmann and Kharasch), 820
- Placenta, 735 (Absts.)
- abruption of, tocographic observations upon patient experiencing (Murphy), 694
- accreta (Jakob), 737 (Abst.)
- direct visualization of, by soft-tissue roentgenography (Dippel and Brown), 738 (Abst.)
- premature separation of (Ballin), 735 (Abst.)
- normally implanted (Fleming), 739 (Abst.)
- previa (Rustia and Tancinco), 736; (Caldera), 738 (Absts.)
- danger of Willett's forceps in (Browne), 740 (Abst.)
- diagnosis of, by cystography (Sala and Bergdolt), 737 (Abst.)
- incidence of, during ten-year period at Cleveland Maternity Hospital (1931-1940), 509
- treatment of (Scott), 738 (Abst.)
- change in, during last 40 years (Winkler and Linden), 736 (Abst.)
- Placenta—Cont'd
- removal of, manual, prontosil in (Pohl), 739 (Abst.)
- roentgenographic visualization of (Vaughn, Weaver, and Adamson), 737 (Abst.)
- Placental blood in treatment of amenorrhea (Halbrecht), 549 (Abst.)
- permeability, study of (Flexner and Gellhorn), 736 (Abst.)
- polyp with severe late puerperal hemorrhage (Dorsey), 591
- transmission of sulfanilamide, toxic manifestations in newborn infant following (Ginzler and Chesner), 46
- Polyp, placental, with severe late puerperal hemorrhage (Dorsey), 591
- Portland Society of Obstetrics and Gynecology, roster of, 181, 741
- Portes cesarean section (Keyes and Whitehouse), 705
- Posterior pituitary sulfonate (pit-sulfonate) in labor, solution of (Dieckmann and Kharasch), 820
- Postmenopausal endometriosis (Frank and Geist), 652
- Powder, glove, use of, complication from (Byron and Welch), 102 (Abst.)
- Pregnancy and endometriosis (Portes and Varangot), 178 (Abst.)
- and labor in patient with cardiac anomaly, probable tetralogy of Fallot (Scherlis and Soloway), 697
- anemia of, macrocytic hyperchromic (Daniel and Antis), 93
- bleeding in first and third trimesters of, treatment of (Stander), 531
- colostrum test for, in prenatal clinic (Pulver and Posner), 690
- complicated by bilateral ovarian dermoid cysts, treated by bilateral oophorectomy (Goodwin), 525
- early diagnosis of, by Friedman-Brouha reaction, aided by transperitoneal ovarioscopy (Crainicianu), 738 (Abst.)
- ectopic, clinical similarity of corpus luteum cyst and (Israel), 22
- twin, unilateral (Lash, and Kaufman), 342
- electroencephalogram in (Gibbs and Reid), 672
- following operation for congenital absence of vagina (Whittemore), 516
- heart disease in, treatment of (Stander), 714
- intrauterine, bilateral ovarian carcinoma associated with (Bosser), 336
- nutrition study in (Williams and Fralin), 647
- ovarian, and eclampsia (Pride and Rucker), 575
- primary (Evans, Sickel, and Ivins), 528
- ruptured (Courtiss), 128
- peritoneal, primary (Studdiford), 487
- pituitary extract during, reactivity to posterior, relation between uterine activity and (Murphy), 117
- renal and ureteral calculi in (Arnell and Getzoff), 34
- selective (Guttmacher), 330 (Abst.)
- test for, prostigmine as, evaluation of (Winkelstein), 231
- toxemia of, experimental production of (Snyder), 1091
- glomerular filtration and renal blood flow in "normal" patients following (Dill, Isenhour, Cadden, and Robinson), 66
- thyroid extract and iodine therapy in, 730 (Correspondence)
- tuberculosis in, unsuspected, problem of (Eisele, Tucker, Vines, and Batty), 183

- Pregnancy—Cont'd  
 urinary infection in, due to Flexner dysenteriae (Diddle and McKee), 481
- Pregnanediol determinations in gynecology and obstetrics (Hamblen, Cuyler, and Baptist), 442
- excretion of, and corpus luteum (Cope), 912 (Abst.)
- glucuronidate determinations, urinary, correlation of vaginal smear studies with (Krohn, Harris, and Hechter), 213
- Premature labor, vitamin E and (Shute), 271
- separation of normally implanted placenta (Fleming), 739 (Abst.)
- of placenta (Ballin), 735 (Abst.)
- Premenstrual distress, electrolyte therapy of (Greenhill and Freed), 548 (Abst.)
- Presidential address at 67th annual meeting of American Gynecological Society, 743
- at fifth annual meeting of South Atlantic Association of Obstetricians and Gynecologists, 553
- Primate animals, studies on, to gynecologic thought (Hartman), 156
- Primigravida, elderly (Wahrsinger and Kushner), 505
- Progesterone and male hormone, mammary carcinoma, response to implantation of (Loeser), 152 (Abst.)
- effect of (Greenblatt, Mortara, and Torpin), 660
- in adolescent girls and young women with functional uterine bleeding (Allen and Heckel), 984
- in treatment of spontaneous abortion (Mason), 630
- urinary estrogens before, during, and after (Smith, Smith, and Schiller), 606
- Prolactin as specific lactogenic hormone (Folley and Young), 358 (Abst.)
- Prontosil in manual removal of placenta (Pohl), 739 (Abst.)
- Prostigmine methylsulfate and delayed menstruation (Winkelstein), 231
- treatment of delayed menstruation with (Grossmann), 549 (Abst.)
- Pseudohermaphroditism, male, clinical, psychiatric and psychoanalytic study of (Finesinger, Meigs, and Sulkowitch), 310
- Pseudomyxoma peritonei (Erving), 492
- Puberty, hemorrhage in, therapy of (Vöge), 546 (Abst.)
- Puerperal morbidity in vaginal trichomoniasis (Trussell, Wilson, Longwell, and Laughlin), 292
- Puerperium, breast engorgement in, methyl testosterone for relief of (Duckman and Turino), 112
- Pulse and respiratory rates during labor as guide to onset of cardiac failure in woman with rheumatic heart disease (Mendelson and Pardee), 370
- Pyometra, bacteriologic study of (Carter), 1074
- Pyrexia, artificial, in pregnant women (Mengert and Paul), 702
- R
- Radiation therapy in obstetrics and gynecology, uses and abuses of (Traut), 638
- Radium in treatment of malignant neoplasms (Traut), 644
- Reaction, tissue, local, comparative, and styptic action of sulfanilamide (Beecham and Friday), 88
- Rectal endometrioma (Bazy, Blondin, and Chene), 178 (Abst.)
- Rectum, injury to, from improperly administered enemas (Ballon and Goldbloom), 212 (Abst.)
- strictured lymphogranulomatous, death due to intraperitoneal rupture of, during parturition (Pollard and Hellendall), 317
- Registry of ovarian tumors, 922 (Announcement)
- Renal and ureteral calculi in pregnancy (Arnell and Getzoff), 34
- blood flow and glomerular filtration in hypertensive woman and in posttoxicemic hypertension (Robinson, Dill, Cadden, and Isenhour), 616
- in "normal" patients following toxemias of pregnancy (Dill, Isenhour, Cadden, and Robinson), 66
- Respiratory and pulse rates during labor as guide to onset of cardiac failure in women with rheumatic heart disease (Mendelson and Pardee), 370
- Resuscitation of newborn infants, apparatus for (Biskind and Eichner), 147; (Alexander and Martin), 351
- Rheumatic heart disease, pulse and respiratory rates during labor as guide to onset of cardiac failure in women with (Mendelson and Pardee), 370
- Roentgen pelvic mensuration, Caldwell-Moloy method of, with correlation of new technical procedures (Taylor), 348
- ray treatment of early puerperal mastitis (Wirth and Peters), 362 (Abst.)
- Roster of American obstetrical and gynecological societies, 181, 182, 741, 742
- Rotation, posterior, of occiput during labor (Klingensmith), 623
- Rupture, ante-partum, of umbilical vein (Silbernagel and Fidler), 712
- intraperitoneal, of strictured lymphogranulomatous rectum during pregnancy, due to (Pollard and Hellendall), 317
- of membranes, diagnosis of, by vaginal smear, identification of fetal squamas and (Bourgeois) 80
- Ruptured ovarian pregnancy (Courtiss), 128
- S
- St. Louis Gynecological Society, roster of, 182, 742
- San Antonio Obstetric Society, roster of, 182, 742
- San Francisco Gynecological Society, roster of, 182, 742
- Sarcoma botryoides of cervix (Fischer and Kantrowitz), 141
- previously treated with irradiation (Scheffey), 932
- Scar endometriosis (Wespi and Kletzhandler), 177 (Abst.)
- Scopolamine in obstetrics (Kirschbaum), 664
- Seattle Gynecological Society, roster of, 182, 742
- Secretion of milk, effect of visible light upon (Menju), 359 (Abst.)
- Semen, vegetative effects of, on female organism (Stemmer), 916 (Abst.)
- Sex hormones and blood pressure (Guirdham), 914 (Abst.)
- female, current status of (Hoskins), 915 (Abst.)
- male, influence of, on female breast (Preisacker), 360 (Abst.)
- therapy, changes in female genital tract during puerperium induced by (Rutherford), 595

- Sexual libido in female (Greenblatt, Mortara, and Torpin), 658
- Shock, allergic, caused by synapoidin (Phillips), 706
- Skull, changes in base of, caused by molding and increased by compression (Moloy), 772
- Society transactions, Chicago Gynecological Society, 171
- New York Obstetrical Society, 542
- Obstetrical Society of Boston, 542
- Obstetrical Society of Philadelphia, 542
- Pittsburgh Obstetrical and Gynecological Society, 171, 543
- South Atlantic Association of Obstetricians and Gynecologists, 734
- Washington Gynecological Society, 171
- Solution of posterior pituitary sulfonate (pit-sulfonate) in labor (Dieckmann and Kharasch), 820
- South Atlantic Association of Obstetricians and Gynecologists, papers of, 553-594
- roster of, 181, 741
- transactions of, 734
- Statistics, department of, 723
- Stilbestrol, experiences with (Abarbanel and Klein), 911 (Abst.)
- in relief of essential dysmenorrhea (Sturgis), 549 (Abst.)
- Sulfanilamide in treatment of venereal lymphogranuloma (Grave and Suskind), 530 (Abst.)
- placental transmission of, toxic manifestations in newborn infant following (Ginzler and Chesner), 46
- powder, use of, in gynecologic and obstetric operations, (Bibb), 464
- styptic action of, comparative local tissue reaction and (Beecham and Friday), 88
- Sulfonamides in treatment of gonorrhea in female (Douglas, Davis, and Shandorf), 1026
- Surgical treatment and postoperative care of vesicovaginal fistula (Miller), 873
- Synapoidin, allergic shock caused by (Phillips), 706
- Synthetic estrogens, use and potency of (Greenhill), 475
- Syphilis, early, treatment of, intravenous drip and other intensive methods for (Eagle and Hogan), 486 (Abst.)

## T

- Teratoma, ovarian, unusual coexistence of granulosa cell tumor and, containing thyroid tissue (Murray, Dockerty, and Pemberton), 134
- Test, colostrum, for pregnancy in prenatal clinic (Pulver and Posner), 690
- for pregnancy, prostigmine as, evaluation of (Winkelstein), 231
- Testosterone in chronic mastitis, local inunction of (Spence), 361 (Abst.)
- in inhibition of lactation, percutaneous use of (Fleischer and Kushner), 361 (Abst.)
- propionate in treatment of mammary pain and secretion (Nathanson, Meigs, and Parsons), 360 (Abst.)
- pellets of, effect of (Greenblatt, Mortara, and Torpin), 661
- suppression of lactation by (Duffy and Corsaro), 361 (Abst.)
- Tetany following prolonged lactation on a deficient diet (Anderson and Brown), 360 (Abst.)
- Tetralogy of Fallot, probable, pregnancy and labor in patient with cardiac anomaly (Scherlis and Soloway), 697
- Texas Association of Obstetricians and Gynecologists, roster of, 182, 742
- Thermo-flo, Newman, conservative treatment of pelvic inflammation with (Falls, Bernell, and Kobak), 240
- Thrombophlebitis, postoperative, bicycle exercises for prophylaxis of, routine use of (Krebs), 73
- Thyroid extract and iodine therapy in pregnancy toxemia, 730 (Correspondence)
- tissue, unusual coexistence of granulosa cell tumor and ovarian teratoma containing (Murray, Dockerty, and Pemberton), 134
- Tissue reaction, local, comparative, and styptic action of sulfanilamide (Beecham and Friday), 88
- Tocographic observations upon patient experiencing a brupt ion of placenta (Murphy), 694
- Toxemia of pregnancy, experimental production of (Snyder), 1091
- followed by glomerular filtration and renal blood flow in "normal" patients (Dill, Isenhour, Cadden, and Robinson), 66
- thyroid extract and iodine therapy in, 730 (Correspondence)
- Transfusion reaction, blood, due to intra-group incompatibility (Crooks), 121
- Transplantation of fascia for relief of urinary stress incontinence (Aldridge), 398
- Trichomoniasis, vaginal (Trussell, Wilson, Longwell, and Laughlin), 292
- Tubal endometriosis, incidence of (Rintelen), 176 (Abst.)
- Tuberculosis in pregnancy, problem of unsuspected (Eisele, Tucker, Vines, and Batty), 183
- of vulva (Barrow and Maxwell), 145
- onset of, clinical relationships between first menstruation and (Nobecourt), 545 (Abst.)
- Tumor, Brenner, bibliography of, 180 (Correspondence)
- bilateral, of ovary (Peale), 138
- connective tissue, rare, in area of Bartholin gland, (Smiley and Kushner), 709
- fibroid, similar, occurring in identical twins (Grosbeck and Pool), 179 (Abst.)
- granulosa cell, unusual coexistence of, and ovarian teratoma containing thyroid tissue (Murray, Dockerty, and Pemberton), 134
- ovarian, registry of, 551, 922
- Twin ectopic pregnancy, unilateral (Lash and Kaufman), 342

## U

- Umbilical vein, rupture of, ante-partum (Silbernagel and Fidler), 712
- Ureter, hormonal influences upon (Hundley, Jr., Diehl, and Diggs), 858
- Ureteral calculi, renal and, in pregnancy (Arnell and Getzoff), 34
- Urinary estrogens before and after injection of estrone into patient with surgical menopause (Smith, Smith, and Schiller), 455
- during and after progesterone, estriol and cyclic administration of progesterone and estradiol benzoate (Smith, Smith, and Schiller), 606
- infection in pregnancy due to flexner dysenteriae (Diddle and McKee), 481

## Urinary—Cont'd

- stress incontinence, transplantation of fascia for relief of (Aldridge), 398
- Uterine activity, relation between, and reactivity to posterior pituitary extract during pregnancy (Murphy), 117
- bleeding, functional, effect of progesterone in adolescent girls and young women with (Allen and Heckel), 984
- pathology of, in climacterium and postclimacterium (Pallos and Treite), 547 (Abst.)
- carcinoma, irradiation treatment of, intestinal injuries resulting from (Aldridge), 833
- contractions, kymograph records of, 355 (Correspondence)
- puerperal (Bickers), 581
- disease, nonmalignant, selective hysterectomy for (Waters), 1107
- fibroids, treatment of, new technique for (Cirio), 180 (Abst.)
- functional hemorrhages, treatment of, by male hormone (Bompard), 916 (Abst.)
- intubation (Bunster), 350 (Abst.)
- mucosa, glycogen estimation in, method of, for clinical purposes (Zondek and Shapiro), 345
- muscle, principle in raspberry leaves which relaxes (Burn and Withell), 354 (Abst.)
- musculature, architecture of (Ivy), 952
- human, effect of follicle hormone on function of (Kneer), 913 (Abst.)
- tonus during labor (Murphy), 694
- Uteroovarian cycle, persistence of, evidence of, in various gynecopathies (Sammartino and Herrera), 544 (Abst.)
- Uteroplacental apoplexy, methods of treating (Rauramo and Kahana), 738 (Abst.)
- Uterus, fibromyomas of, etiologic and pathologic factors in series of 1,741 (Torpin, Pund, and Peebles), 569
- irradiation of, for benign conditions, malignancy subsequent to (Scheffey), 925
- Utopian obstetrics (Bartholomew), 553

## V

- Vaccine, bacillus coli, treatment of pelvic inflammatory disease with intradermal administration of (Krieg), 681
- Vagina, congenital absence of, pregnancy following operation for (Whittemore), 516
- medication of, improved vehicle for (Williams), 153
- partial congenital aplasia of (Dannreuther), 1063

- Vaginal iontophoresis of choline compound (Jacoby and DerBrucke), 250
- smear changes, correlation of, in estrogenic treatment of menopausal symptoms and senile vaginitis (Ottoway), 915 (Abst.)
- correlated to ovarian function (Bennett and Russell), 919 (Abst.)
- in diagnosis of ruptured membranes, identification of fetal squamas and (Bourgeois), 80
- studies, correlation of, with urinary pregnanediol glucuronidates determinations (Krohn, Harris and Hechter), 213
- trichomoniasis (Trussell, Wilson, Longwell and Laughlin), 292
- Vaginitis, senile, and menopausal symptoms, correlation of vaginal smear changes in estrogenic treatment of (Ottoway), 915 (Abst.)
- senile, estrogens in treatment of (Buxton), 109
- Vegetative effects of semen on female organism (Stemmer), 916 (Abst.)
- Venereal lymphogranuloma, treatment of, with sulfanilamide (Grace and Suskind), 530 (Abst.)
- Vesicovaginal fistula following total hysterectomy, partial colpocleisis, an approach to (Holden), 880
- surgical treatment and postoperative care of (Miller), 873
- Vitamins B<sub>1</sub> and B<sub>6</sub> in treatment of nausea and vomiting in pregnancy (Willis, Winn, Morris, Newsom, and Massey), 265
- C deficiency as possible factor in pathogenesis of erythroblastosis fetalis (Burnham), 920 (Correspondence)
- E and premature labor (Shute), 271
- K, does antenatal use of, prevent hemorrhage in newborn infant (Parks and Sweet), 432
- Vomiting and nausea in pregnancy, treatment of, with vitamins B<sub>1</sub> and B<sub>6</sub> (Willis, Winn, Morris, Newsom and Massey), 265
- Vulva, tuberculosis of (Barrow and Maxwell), 145

## W

- War effort, women in, 732 (Editorial)
- Washington Gynecological Society, roster of, 182, 741
- transactions of, 171
- Wisconsin Society of Obstetrics and Gynecology, roster of, 182, 742
- Women in war effort, 732 (Editorial)

## X

- X-ray in treatment of malignant neoplasms (Traut), 644



Robson<sup>4</sup> registered the activity and reactivity of pieces of human uterus removed at various stages of pregnancy. No specific type of activity was discovered at any particular period, and at no stage of pregnancy investigated was there any definite degree of rhythmicity observed. High and low degrees of rhythmicity occurred both early and late in pregnancy. Tissue secured at the earliest periods reacted only to large amounts of extract, and no correlation was found between the character of the spontaneous contractions, and those inaugurated by the extract. Strips of muscle removed from different parts of the same uterus exhibited marked differences in activity, though their reactivity was substantially identical.

### Percentage of Tracings

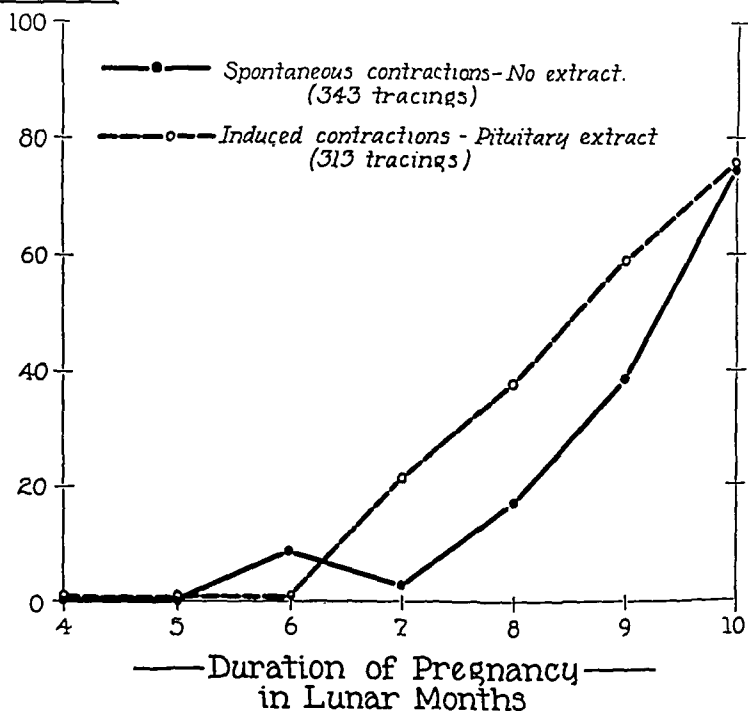


Fig. 1.—Abscissa denotes duration of pregnancy in lunar months. Ordinate indicates the percentage of tocographic tracings listed in Table I, which exhibited: (a) Spontaneously arising uterine contractions, or (b) ones resulting from the administration of posterior pituitary extract. Note parallelism in occurrence of the two types of contractions.

### MATERIALS AND METHODS

The present observations upon activity and reactivity were made directly upon patients. Two hundred women attending the Maternity Department of the Hospital of the University of Pennsylvania supplied records of spontaneous contractions, and 32 patients residing in a Maternity Home made possible records of reactivity.

In both groups of patients the uterine contractions were registered with a Lóránd tocograph. This is a mechanical device which supplies a graphic record of uterine movements detected through the medium of the anterior abdominal wall.<sup>6</sup>

We wish to thank the Schering Corporation of Bloomfield, N. J., for their kindness in supplying the Oreton M, their brand of oral methyl testosterone, which has been used exclusively in this study.

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## THE RELATION BETWEEN UTERINE ACTIVITY AND REACTIVITY TO POSTERIOR PITUITARY EXTRACT DURING PREGNANCY

A STUDY OF 656 RECORDS MADE WITH THE LÓRÁND TOCOGRAPH

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THE spontaneous activity of the uterus and its reactivity to posterior pituitary extract during pregnancy have been studied in strips of uterine muscle removed from both human beings and animals, and upon the latter in vivo. As far as can be ascertained, however, neither type of movement has been studied systematically in patients.

Robson<sup>1</sup> studied activity and reactivity in strips of muscle removed from the rabbit. He found no definite type of activity at any of the stages of pregnancy investigated, and no direct relation between activity and reactivity. He measured reactivity in terms of the minimum amount of extract necessary to initiate contractions. By this method he confirmed the observations of Knaus,<sup>2</sup> that reactivity to large doses is absent in the first half of pregnancy, but is present later. The exact time at which it appeared, and the minimum amount of extract necessary to cause contraction varied from animal to animal. Once established, however, reactivity increased, and was found to be always high at parturition.

Robson observed considerable variation in the degree of reactivity of different uteri at parturition, and even in different parts of the same organ. Several times at parturition he noted high degrees of rhythmicity. He believed that the differences in reactivity which he noted were outside of the limits of experimental error.

Robson and Schild<sup>3</sup> studied the spontaneous contractions of the pregnant uterus of the cat in vivo and in vitro. In this animal they found a progressive increase in uterine sensitivity as pregnancy advanced.



## COMMENT

Robson determined the minimum amount of extract necessary to initiate contractions; since it decreased progressively as pregnancy advanced, he concluded that uterine sensitivity increased.

We found that an increasing number of patients exhibited both activity and reactivity as pregnancy advanced. We also observed at any given period in pregnancy that an increase in the dose of the stimulant made more individuals react. These observations lead us to conclude also, that sensitivity increases as pregnancy advances.

Up to the present writing we have assembled some 1,400 tocographic records of the uterine contractions of pregnancy. An analysis of this material leads to the following statements, which also confirm, to some extent, previous observations of Robson: Spontaneous uterine activity is an extremely variable quantity during pregnancy. Uterine contractions may be absent for periods as long as an hour, late in pregnancy as well as very early. Spontaneous contractions occur with great irregularity throughout the most of pregnancy, at least until the last several weeks. Exceptions have been noted, since we have observed extreme rhythmicity in the earliest tracing which we made.

Reactivity to posterior lobe extract varies widely from patient to patient both as regards the time that it first appears and in the amount necessary to initiate contractions.

## SUMMARY AND CONCLUSIONS

1. The frequency of occurrence of uterine contractions arising spontaneously, and of those contractions induced by the intramuscular administration of posterior pituitary extract was studied in a group of pregnant women, between the one hundred and tenth and two hundred and seventy-ninth day of gestation, by means of the Lóránd tocograph.

2. Spontaneous contractions were recorded for the first time during the sixth lunar month, and induced contractions during the seventh lunar month of pregnancy.

3. The proportion of records registering activity and reactivity increased progressively as pregnancy advanced, running parallel to each other.

4. From these observations it is concluded that the sensitivity of the pregnant human uterus to posterior pituitary extract increases progressively as pregnancy advances.

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Each tracing was made with the patient in the recumbent posture, following a rest period of ten minutes. In the study of spontaneous contractions, the recording period lasted thirty minutes. The degree of activity was measured in terms of whether or not any spontaneous contractions were recorded.

Reactivity was measured in terms of whether or not the administration of posterior pituitary extract initiated contractions. In this instance the recording period lasted thirty minutes following the administration of the drug.

The patients upon whom reactivity was studied were admitted to the Maternity Home at various periods during middle and late pregnancy. Each patient was observed and tested once a week. The treatment consisted of an intramuscular injection of posterior lobe extract (obstetric pituitrin, Parke, Davis & Co.), the same dose being employed each week. Fifteen patients received a weekly dose of 3 minims, nine a dose of 2 minims and four a dose of 1 minim. Complete details of treatment and their results have been reported elsewhere.<sup>5</sup>

#### RESULTS

The number of tracings made for the purpose of registering activity and reactivity are listed in Table I, according to the duration of pregnancy. The percentages of the tracings, which registered either activity or reactivity, are shown in graphic form in Fig. 1.

TABLE 1. SHOWING THE MONTHLY DISTRIBUTION OF TOCOGRAPHIC RECORDS SECURED FROM A SERIES OF PREGNANT WOMEN, ARRANGED ACCORDING TO WHETHER OR NOT POSTERIOR PITUITARY EXTRACT WAS ADMINISTERED WHILE THE RECORDING WAS IN PROGRESS

| LUNAR MONTHS OF PREGNANCY | POSTERIOR PITUITARY EXTRACT |              |
|---------------------------|-----------------------------|--------------|
|                           | NOT ADMINISTERED            | ADMINISTERED |
|                           | Tracings                    | Tracings     |
| 4                         | 1                           | 1            |
| 5                         | 6                           | 9            |
| 6                         | 12                          | 12           |
| 7                         | 38                          | 26           |
| 8                         | 19                          | 64           |
| 9                         | 44                          | 93           |
| 10                        | 223                         | 108          |
| Total                     | 343                         | 313          |

From the graph, it is apparent that activity appeared earlier in pregnancy than did reactivity. Following their onset the proportion of tracings which registered activity and reactivity increased progressively, and at the same rate of increase. More tracings recorded induced contractions than spontaneous ones. This fact no doubt depended upon the dosage of the oxytocic agent. The significant characteristic of the graph is the parallelism between the increases in activity and reactivity.

Another interesting characteristic of the graph is the observation that more than 20 per cent of the tracings in both groups, failed to register either activity or reactivity in the tenth lunar month.

The blood selected for the transfusion after a careful cross-matching, was Group 0 from a bank blood three days old. Approximately 450 c.c. had been given when the patient had a mild chill that was easily controlled by heat. She was given 250 c.c. of 1½ per cent sodium bicarbonate. The following morning she was desperately ill with a generalized peritonitis and marked icterus. The pelvic mass previously noted could not be felt. The urine showed the presence of bile with urobilogen positive 1 to 40. The benzdine test was negative. Microscopically, no red or white cells were found. The icterus index was 125 mg. per cent. Urea nitrogen was 9.8 mg. per cent. There was no urinary suppression. Cholesterol was 101 mg. per cent. Cholesterol esters were 38 mg. per cent.

Clinically, it was felt that the pelvic mass had ruptured, either due to the vaginal examination or spontaneously and had caused a generalized peritonitis. The jaundice was ascribed to the use of bank blood, or to the sulfathiazole.

During the next twelve days the icterus gradually cleared up. The white blood count remained high, but there was a drop of the red blood count to 2,940,000 and hemoglobin to 50 per cent. The pelvic infection localized and pointed suprapubically. A celiotomy was performed under local anesthesia and a large amount of pus was evacuated from a pelvic abscess.

Due to the poor condition of the patient a second transfusion was considered imperative. This time warm fresh citrated blood was used in order to avoid another reaction. Four hundred and fifty cubic centimeters of blood were introduced, when once again the patient developed a chill followed by a rise in temperature to 106° F. The urine contained bile and urobilogen in dilution of 1 to 20. No hemoglobinuria was noted, but there was some urinary suppression. The urea nitrogen was 37 mg. per cent. A generalized icterus was present. The heterophile antibody reaction was negative and the cell fragility test was well within normal limits.

Because of the two transfusion reactions, it was felt that some unrecognized incompatibility existed which required further investigation. A study by Wiener and Forer, since reported,<sup>1</sup> showed the patient's blood to be Group 0, Type N, Rh negative and to contain two distinct irregular isoagglutinins, namely, anti-Rh and anti-M, which reacted with the donor's blood and caused the severe reactions noted above. Auto-agglutination was ruled out by the absence of agglutination in mixtures of the patient's cells and serum. Accordingly Group 0 donors were sought who belonged to Type N and were Rh negative. Not until 28 donors had been tested was the proper donor obtained. The donor selected was Group 0, Type N, Rh negative, and 500 c.c. of his blood were given without any reaction. Two weeks later another transfusion, from the same donor, was given without incident. The patient subsequently received three transfusions without reaction from two donors selected by Dr. Wiener.

During the following two months, the resistance of the patient was increased by the aid of transfusions and general supportive therapy. On two occasions the pelvic abscesses re-formed and were drained by posterior colpotomies. Subsequently a laparotomy was performed and a

## BLOOD TRANSFUSION REACTION DUE TO INTRA-GROUP INCOMPATIBILITY\*

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REPEATED small blood transfusions have often proved to be life-saving measures in the treatment of chronic pelvic infections, but their use has some danger, notwithstanding blood typing and cross-matching. In the case to be reported a marked reaction developed following transfusion of blood found to be compatible by the usual laboratory methods. Further investigations revealed the reaction to be due to factors that could not be detected by these ordinary methods.

M. M. (Case No. 107616), female, white, aged 34 years, was admitted to Morrisania City Hospital on April 3, 1941. Two weeks previously a posterior colpotomy had been done at another hospital to drain a pelvic abscess. The cause of this abscess was not definitely established. She left the hospital improved but soon afterward developed a recurrence of low abdominal pains associated with chills and fever and was referred to Morrisania City Hospital.

The previous medical history was negative. Past surgery consisted of a curettage in 1938 for a spontaneous incomplete abortion. Menarche began at 14 years of age, regular, every twenty-eight days, lasting seven to eight days. The last menstrual period occurred, March 1 to 8, 1941. She had been delivered of three children; all were uncomplicated spontaneous full-term deliveries.

Physical examination revealed an acutely ill patient, temperature 105.6° F., pulse 136, and respirations 36. The skin was warm and dry. The heart and lungs showed no abnormalities. The abdomen was tense. There was marked abdominal tenderness with rebound tenderness in both lower quadrants. A profuse foul-smelling vaginal discharge was present from a healing colpotomy wound posterior to the cervix and a mass approximately 8 cm. in diameter in the left adnexal region. It was fairly firm, fixed, and extremely tender. The opposite adnexa were thickened and tender. The uterus was slightly enlarged, soft, smooth, and tender on motion.

The blood Wassermann was negative; hemoglobin, 55 per cent; red blood count, 3,140,000; white blood count, 26,000; polymorphonuclears, 82 per cent; lymphocytes, 18 per cent; sedimentation time, 18 mm. in six minutes; urine, negative; blood culture, negative.

The clinical diagnosis was left tuboovarian abscess with pelvic peritonitis.

Treatment consisted of forced fluids, Fowler's position, and sulfathiazole. The patient was typed for the first of a number of small blood transfusions and found to be Group 0 (Landsteiner), Group 4 (Moss), or Group 1 (Jansky).

\*Presented at a meeting of the New York Academy of Medicine, Section on Obstetrics and Gynecology, November 25, 1941.

# IMMEDIATE POST-PARTUM REPAIR OF OLD PERINEAL LACERATIONS

## A SURVEY OF PERSONAL EXPERIENCES WITH NOTES ON INDICATIONS AND LIMITATIONS OF THE PROCEDURE

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THE perineal structures are the most abused in the birth tract during parturition. This is true in normal births as well as with instrumental procedures, although perineotomy lessens residual trauma. In addition, the perineum often matches the abdominal wall in the inadequacy of post-partum involutional change. One may therefore expect to find in most multiparous patients, perineums which are (1) torn to varying degree, with or without associated rectocele and less frequently cystocele, or (2) generally relaxed from involutional failure after parturitional overdilatation. Post-partum examinations made by any observant physician confirm the frequency of these findings. Even "normal spontaneous delivery" of a small fetus is followed on occasion by pelvic relaxation totally disproportionate to the probable trauma.

Consequently, when the past history of the pregnant woman indicates previous damage, either by character of labor, size of fetus, instrumental intervention, or puerperal morbidity, one looks for and commonly finds residual parturitional trauma of varying degree.

The question posed for the physician now is this, "Is it safe, feasible and recommendable to repair old pelvic lacerations of varying degree immediately following subsequent childbirth?"

It has been customary over many years for one of us (E. G. W.), assuming the answer of the question to be "yes," to repair such old lacerations and relaxations immediately post partum.

To assess more rationally the validity of such an assumption, we have carefully followed a group of patients upon whom reparative operations were performed during the past five years (Table I).

### CLASSIFICATION OF CASES

In an analysis such as this, an astute reader may question the sorting of cases. Accordingly it is expedient to indicate clearly our position regarding the method of allocation. We regard as second-degree perineal

tuboovarian abscess on the left side removed. The patient made an uneventful recovery. Follow-up examination revealed the patient in good health.

#### COMMENT

In 1940 Landsteiner and Wiener<sup>2</sup> reported the presence of an agglutinin which was developed in the sera of rabbits by the injection of blood from the *Macacus rhesus* monkey. The sera when tested with human blood showed the presence of a new agglutinable substance in the red blood cells. They called this the Rh or rhesus factor. Since then it has been found that 85 per cent of human beings of the white race have the Rh factor, and are called Rh positive. The remaining 15 per cent who do not have this factor are referred to as Rh negative.<sup>3, 4</sup>

The role of the Rh factor as the cause of blood transfusion reactions may be explained as follows: An Rh negative mother bears a fetus that has inherited the Rh antigen from an Rh positive father. The factor is inherited as a dominant property.<sup>4</sup> The antigen of the fetus diffuses through the placental barrier and stimulates the formation of anti-Rh agglutinins in the mother's blood.

Should the mother require a transfusion and a Rh positive donor is used, agglutination and hemolysis of the transfused blood will occur due to the presence of the anti-Rh agglutinins.

This explanation does not explain all blood transfusion reactions, but it is a likely answer to reactions that occur in women who are Rh negative and have borne Rh positive children. The presence of anti-Rh agglutinins may be readily determined by the method of cross-matching recommended by Levine.<sup>5</sup> The mixture of patient's serum and donor's cells is incubated for thirty minutes at 37° C. and then centrifuged at low speed (500 r.p.m.) for one minute. The anti-Rh agglutinin usually reacts better at 37° C. than at room temperature. The simplicity of the procedure warrants its use before giving a transfusion to any woman who has been pregnant, or who has previously received a blood transfusion. If a woman has never been pregnant but for some reason received a transfusion from a Rh positive donor, enough anti-Rh agglutinins may be formed as to cause a transfusion reaction at a subsequent time if the same or any other Rh positive donor is used again.

#### SUMMARY

A case is presented in which a patient suffered two severe blood transfusion reactions, due to anti-Rh isoagglutinins. By selecting donors of the same group who were Rh negative, five transfusions were given without incident.

I wish to express my thanks to Dr. A. Tamis and Miss Helen Samlowitz for their aid in the composition of this paper.

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Not shown in the table are 9 cases of cystocele repaired immediately after childbirth. While not properly encompassed in this presentation, they are recorded here to allow of pertinent comment later.

#### TYPE OF REPAIR

It would be reckless to say that repair technique is standardized, since each operation and more especially each operator is individualized. Basically, all good perineal operations are alike. They consist in resection and reposition of lacerated and divided tissues and resection or reduplication of overstretched and attenuated structures. This means resuturing the levator ani muscles, re-forming the rectovaginal septum, and restoring the structures of the urogenital diaphragm. With third-degree lacerations, clear identification and resuture of the torn sphincter ends is the all-important additional requirement to those cited. All operations in this study were designed to effect such ends. Chromic catgut No. 0 or No. 00 was used throughout, except for No. 1 in the levator ani and sphincter ani. In two third-degree repairs, silver wire was used through the sphincter ani, with no greater satisfaction or convincing evidence of indispensability.

The use of fine catgut and a minimum of buried knots unquestionably results in greater ease for the patient, less tissue reaction and infection, and sounder healing. Yet, the repair is more difficult at this time than in the nonparturient. The field is obscured by blood from the uterus and highly vascularized tissues. Large varices are more commonly encountered. Hemostasis, more difficult, assumes excessive importance in anemic, debilitated, or profusely bleeding patients. The tissues are easily recognizable by those thoroughly familiar with the field, but the sutures must be carefully placed, with proper tension, in the succulent structures.

#### ANALYSIS OF DATA

Except for Group I, in which local anesthesia was used in about 20 per cent of the cases, spinal anesthesia was most commonly utilized. Dissolved in 3 c.c. of spinal fluid, 50 mg. of novocain crystals in the fourth lumbar space was the usual amount. Gas-ether was used in approximately 30 per cent of the entire group.

Thirteen, or 9 per cent, of the entire number were morbid. Not all morbidity was ascribable to the operation performed. Little hazard seemed to be added to the parturition just experienced, since only 5 became locally infected, and there were only 3 complete breakdowns. There were no deaths.

Our post-partum care consists mainly in cleanliness. Intravaginal antisepsis is rarely resorted to but neither is it derided. It is our belief that from a bacteriologic standpoint the vaginal structures have not forgotten that they were once part of a cloaca, and are ordinarily re-

lacerations all those involving the perineal body which result in partial or complete separation of the musculofascial structures from the bulbo-cavernosus muscles to the sphincter ani. The divulsion of the bulbo-cavernosus (constrictor cunni) muscles permits a "marital gaping" of the introitus which becomes progressively more patent, as the rent involves more of the structures in the urogenital diaphragm. With practically all such lacerations there is a rectocele evincing perirectal fascial damage of some degree. The posterior vaginal support is weakened and the "rectocele" ranges from a mucosal overhang to a gross fascial defect with complete herniation of the anterior rectal wall. Since it is a not unreasonable assumption that the causative instrumentality (heredity, progeny or steel) will permit of damage to lower vaginal tissues as easily as perineal, the end result of rectal wall damage depends upon other factors. These are the extent of the initial lesion, competence of the repair immediately effected, the adequacy of involution, and the post-partum state of activity. Inasmuch as the corrective procedures (and likewise the operative hazards) for the different types of posterior

TABLE I. IMMEDIATE POST-PARTUM REPAIR OF OLD PERINEAL LACERATIONS

|              |   | NUM-<br>BER | MOR-<br>BID | IMMEDIATE<br>RESULTS  |               | LATE FOLLOW-<br>UP |          |                | P.O.<br>DYSPA-<br>REUNIA |
|--------------|---|-------------|-------------|-----------------------|---------------|--------------------|----------|----------------|--------------------------|
|              |   |             |             | PRI-<br>MARY<br>UNION | IN-<br>FECTED | 4<br>WK.           | 3<br>MO. | RESULT<br>GOOD |                          |
| GROUP<br>I   | 1. 2° Perineal lac-<br>eration and<br>rectocele | 75          | 4           | 73                    | 2             | 69                 | 71       | 67             | 4                        |
|              | 2. 3° Perineal lac-<br>eration                  | 6           | 2           | 5                     | 1             | 6                  | 6        | 5              | 1                        |
|              | Total   | 81          |             |                       |               |                    |          |                |                          |
| GROUP<br>II  | 1. 2° Perineal lac-<br>eration and<br>rectocele | 43          | 3           | 42                    | 1             | 42                 | 39       | 36             | 3                        |
|              | 2. 3° Perineal lac-<br>eration                  | 2           | 1           | 2                     |               | 2                  | 2        | 1              | 1                        |
|              | Total   | 45          |             |                       |               |                    |          |                |                          |
| GROUP<br>III | 1. 2° Perineal lac-<br>eration and<br>rectocele | 20          | 2           | 19                    | 1             | 20                 | 19       | 14             | 5                        |
|              | 2. 3° Perineal lac-<br>eration                  | 2           | 1           | 2                     | 0             | 2                  | 2        | 2              |                          |
|              | Total   | 22          |             |                       |               |                    |          |                |                          |
|              | Grand Total                                     | 148         | 13          | 143                   | 5             | 141                | 139      | 125            | 14                       |

vaginal wall relaxation are essentially the same, in this study all were grouped with the second-degree perineal lacerations. Third-degree perineal lacerations here include all complete disruptions of the perineum, involving the sphincter ani and combined with various degrees of fecal incontinence. In several instances the partially healed rent involved the anterior rectal wall.



2. Reparative operation is especially recommended for a symptom-producing condition in a patient fearing or unable to afford rehospitalization at a more propitious time.

3. Although later operation is cleaner and less bloody, and allows a better technique, there is little added risk from immediate operation, and the morbidity incidence is low.

4. Perineal infection was noted in 5 of 148 reparative operations, and the repair broke down completely in three of these.

5. The outstanding postoperative complication is dyspareunia and this is avoidable.

6. Immediate post-partum repair of cystocele is much less satisfactory and offers reasonable probability of effective correction only in selected cases and in expert hands. It is not without danger and more satisfactory results are generally obtained by later operation.

## RUPTURED OVARIAN PREGNANCY

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IN THE eighteen years, from October 1, 1923, to October 1, 1941, a total of 24,733 pregnant patients were treated at the New England Hospital for Women and Children. These cases were classified as follows:

|                                | NUMBER | PER CENT |
|--------------------------------|--------|----------|
| Delivered (term and premature) | 23,133 | 93.53    |
| Miscarriages                   | 1,494  | 6.04     |
| Ectopic pregnancies            | 106    | 0.43     |
| Total pregnancies              | 24,733 | 100.00   |

However, of all the extrauterine pregnancies recorded at this hospital, the case to be reported in detail below is the only ovarian pregnancy found. The incidence in proportion to the total number of ectopic pregnancies is 0.94 per cent, and the rate of occurrence in relation to the total number of pregnancies is 1 in 25,000.

This case of ovarian pregnancy presents all of the classical features required for the definitive postoperative diagnosis of such cases, as enumerated by Spiegelberg.

A review of the literature of the past ten years shows a great increase in interest in the subject of ovarian pregnancy. In 1932, Wollner<sup>1</sup> published a case of ovarian pregnancy and offered some interesting comments on its etiology. In addition, he carefully scrutinized the previously reported cases and found that only 48 of the 87 cases were acceptable as primary ovarian pregnancies. Gandy<sup>2</sup> and Hyams<sup>3</sup> also reported cases and offered suggestions as to the etiologic factors. Though we accept these explanations, it has been suggested that perhaps many of the reported cases may actually represent tubal pregnancy with complete abortion,<sup>4</sup> an idea not generally accepted.

sistant to fecal contamination. The bowels therefore are not "tied up," but normal movements encouraged and low enemas used. Catheterization is dispensed with unless bladder atony appears or pyelocystitis is present.

Analgesics for pain are not commonly needed. Moist heat in the form of witch hazel or saline applications or flaxseed poultices is generally better received than dry heat. Short wave therapy brings pain relief and subsidence of congestion in nonsuppurative perineal inflammation. It is regularly used when there is actual or suspected endometritis.

On follow-up examination, 141 patients were seen in four weeks, and 139 three months post partum. The result was recorded as "good" in 125 of the 148 operations done. This means the patient was relieved of any symptoms reasonably ascribable to the old perineal damage, and had an anatomically restored lower vaginal tract. She was also free of any symptoms reasonably chargeable to the operative procedure itself. Fourteen patients complained of dyspareunia. In all cases the introitus was too tight and in 6 cases it was of the "dashboard" type. A number of patients had vaginal constriction but no marital complaints, and subsequent physiologic dilation may be assumed. Irrespective of accuracy of anatomic repair, dyspareunia is considered a highly objectionable complication and largely avoidable. It is likely to follow if there is excessive removal of redundant vaginal musculo-fascial tissues, if the levators are too broadly "blocked" together, or if a high "dashboard" perineum is built up at the expense of an adequate vaginal orifice. The surgeon must remember the physiologic assistance of involutional change in the post-partum vagina, in estimating the degree of operative constriction of the vagina and the introitus. Overzealous reduction of orificial and vaginal capacity is the leading cause of subsequent dyspareunia.

The 9 cystocele repairs done immediately post partum were of unusual interest because of the difficulties experienced. It was found that patients cannot be positioned properly; the flaccid, edematous cervix tears easily and bleeds freely with traction; and it is difficult to keep the field clear. The dissection itself in the highly vascular field is bloody, and the tissues friable and not clearly recognizable. Shortening of the anterior vaginal wall was noted in one case and the cystocele repair was deficient in two others. In the other six, the operating technique was less flattering to the surgeon's ego than the results as observed some months later. These were noted to have been satisfactory.

#### SUMMARY

1. Immediate post-partum repair of old perineal lacerations is a safe and feasible gynecoplastic procedure.

episodes during the past few years of pain in the left lower quadrant on walking and working, but this persisted only one day at a time. The genitourinary history contributed the fact that dysuria, lasting one week, occurred five years ago, with a probable diagnosis of pyelitis, and recurred one month ago. There was no history of gonorrheal infection. The cardiorespiratory systems were essentially normal.

The physical examination revealed a well-developed, but pale and thin, female in an apprehensive state. Pupils were equal and reacted to light and accommodation. Breasts had a slightly pigmented areola, but no masses or tenderness, and a healed scar on the right breast. Blood pressure was 100/68. The abdomen revealed generalized tenderness, especially in the left lower quadrant. There was a palpable mass over the region of the right adnexa which was the size of an egg. Spasm and rebound tenderness were elicited in both lower quadrants. There was a healed right rectus incision. The liver, spleen, and kidneys were not palpable. The reflexes were bilaterally hyperactive, and the extremities were normal.

Pelvic examination revealed a marital outlet and no posterior or anterior relaxation. No vulvovaginal or urethral infection were noted. The cervix was soft and presented some suggestion of cyanosis. The uterus was somewhat enlarged and soft, with no irregularities to suggest myoma, but displaced slightly to the right. In the right adnexa was a mass about the size of an egg and somewhat tender. In the left adnexa, another mass, about the same size as that on the right, was present and distinctly tender. There was some pain on moving the cervix to the right. Because she did not wish to go to the hospital for further study, she was allowed to go home, remaining under constant care of a nurse. A Friedman test was done the following morning, but the rabbit died immediately. Another test repeated the following morning killed a second rabbit, and a third done the next morning with small doses of urine was reported as positive.

Until October 9 the patient remained fairly comfortable with occasional slight staining. On this day she was suddenly seized with a severe, sharp, agonizing pain in the left lower quadrant. There was no associated nausea or vomiting. Abdominal examination revealed the presence of a definite mass in the right lower quadrant. The vaginal examination had not changed except that tenderness was greater and was most marked over the palpable abdominal mass. The abdominal mass in the left lower quadrant was the same size. Hospitalization was immediately advised.

*Laboratory Studies.*—Blood specimen on admission revealed a hemoglobin content of 12 Gm. by the Sahli standard; red blood count, 4.51; white blood count, 7.650, with a differential count of 61 polymorphonuclears, 26 lymphocytes, 6 monocytes, 5 basophiles, and 2 eosinophiles. The urine was yellow, cloudy, and acid with a specific gravity of 1.006 with no albumin or sugar. A centrifuged sediment contained 1 to 3 white blood cells per high power field and some large epithelial cells.

The preoperative diagnosis was ectopic pregnancy on the left and twisted ovarian cyst on the right.

*Operative Procedure.*—Under spinal anesthesia, a midline suprapubic incision was made. On opening the peritoneal cavity 50 c.c. of free blood was found with considerable clotted blood. The omentum was

Miller and Heimark<sup>5</sup> have commented on the discrepancy between the figures of various authors on the frequency and incidence of this condition. It is felt that the literature is incomplete and confusing and only by the successive reports will the true incidence be discovered. Young and Hawk<sup>6</sup> reported cases of ovarian pregnancy with an incidence of 0.7 per cent of all uterine pregnancies in their series of 148 cases. Jordan and others<sup>7</sup> mention Strezoff who found only one secondary or superficial case in 350 extrauterine pregnancies, and Zimmerman who had two cases out of 120 ectopic pregnancies, with only one acceptable as primary intrafollicular pregnancy. In Cosgrove's experience, only one uncertain primary ovarian pregnancy is mentioned, but Randall and Wellbrock<sup>9</sup> report a case and state that the incidence at the Mayo Clinic is 2 of 400 ectopic pregnancies.

Jordan and others<sup>7</sup> have presented one of the most complete histologic descriptions of this type of case. They mention the histologic development of such an entity and differentiate between primary and secondary ovarian pregnancy. They speak of intrafollicular and extrafollicular or superficial ovarian pregnancy types.

Numerous other case reports by various authors<sup>10-12, 16-22, 23-33</sup> bring the total of cases reported in the American and English literature to 40. If we add Wollner's 48 cases, and the one to be discussed below, we thus have a total of 89 cases of this rather rare condition, thus forming a good nucleus for further study of this most interesting pathologic entity.

#### CASE REPORT

This 26-year-old white patient, married for seven years, was first seen at the office on Sept. 30, 1941, with a complaint of staining for the previous three weeks. She had begun to menstruate at eleven, and her periods always occurred every twenty-six to twenty-eight days. She would flow for five days with moderate dysmenorrhea on the first and second days. Her last normal period started on July 28, 1941.

On Aug. 15, 1941, she experienced an attack of severe abdominal pain. The physician who examined her felt that she had a "bowel disturbance," and advised the administration of a soapsuds enema. Five days later, on August 20, a brown vaginal discharge appeared which persisted for two weeks. Then she had an episode of profuse dark red bleeding which continued for two days, on September 3 and 4. The bleeding and staining then stopped for two weeks until September 19, when they recurred. This staining persisted until the time she presented herself for examination. During the previous month, the patient had experienced no digestive disturbance except nausea, and the only urinary symptom was frequency.

The family history and social history were noncontributory. The past history revealed the fact that an appendectomy was performed eleven years before without any postoperative complications. Two years ago the patient had had a right breast tumor removed, which was diagnosed as a lipoma. Since the patient was desirous of becoming pregnant, a hysterosalpingography was performed two years ago and the patient was informed that she could not become pregnant. There was no history of any serious medical illnesses. The gastrointestinal history revealed that the appetite was good but the bowels were slightly constipated. There was no history of vomiting or of bloody or tarry stools. Jaundice and postprandial discomfort were absent. There had been

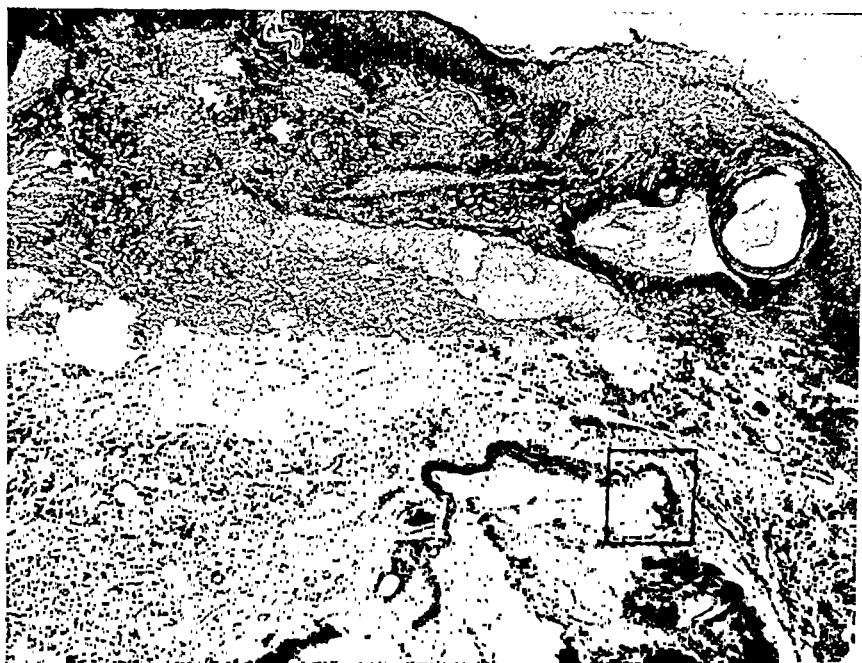


Fig. 1.—Cortex of the right ovary, showing site of implantation of the ovum and blood clot.  $\times 60$ .



Fig. 2.—Magnification of blocked area in Fig. 1, with a villus and decidua.  $\times 160$ .

#### SUMMARY

A case of ovarian pregnancy in a young woman of 26 years, with a description of the pathologic specimens, is reported in detail, and the literature to date is discussed.

adherent to the parietal pelvic peritoneum. When this was dissected free, the pelvic organs were exposed. The uterus was slightly enlarged and not discolored. The left ovary was normal except for a thin-walled solitary cyst containing dark-colored fluid. On inspection the right ovary proved to be the seat of pathology. It was approximately 3 by 3 by 2 inches in size, and at its upper pole there was a ragged tear about one inch long, from which there was a constant ooze of blood. This tear communicated with a cavity that was filled with a blood clot. The possibility of an ovarian pregnancy was considered and the ovary inspected again. It was found to have its normal attachments and relations and to be entirely free of its tube. Both tubes were carefully inspected, and no sign of any pathologic change could be seen or palpated. The entire right ovary was removed and its pedicle was doubly ligated. The cyst of the left ovary was resected and the bleeding was controlled with fine ligatures. The peritoneal cavity was carefully cleaned of blood and clots, and the abdominal wall was closed in layers without drainage.

The patient made an uneventful convalescence and was discharged on the fourteenth postoperative day.

*Discharge Diagnosis.*—Ruptured right ovarian pregnancy and solitary cyst of left ovary.

The report of Dr. G. Lindh Muller, the hospital pathologist, was as follows:

*Pathologic Examination.*—(No. P-41-1325.) Specimen consisted of the right ovary and a portion of the left ovary. The right ovary was an irregular mass, 7.5 by 7 by 4.5 cm. in size, with a ragged tear at one pole. The surface of the intact portion was reddish in color and slightly nodular. In one area a few small translucent cysts were seen. The interior of the cystlike mass was filled with large amounts of dark-clotted blood. Cut sections of the wall revealed a rim of recognizable ovarian tissue which contained hemorrhagic areas and a few small cysts filled with clear fluid. Grossly there was no evidence of placental tissue and no embryo was seen.

*Microscopic Examination.*—Sections from the periphery of the mass showed ovarian stroma with a developing follicle and small atresic follicles. Several corpora albicantia were present. Adherent to this shell of ovarian tissue was a partly degenerated blood clot with some fibrinous strands. It contained shadow-like degenerated chorionic villi. In several sections well-preserved chorionic villi and small areas of decidual cells were present. Such a section is illustrated in Fig. 1, which shows the cortex of the ovary with a developing follicle and several corpora albicantia. In the lower right portion of the section is the partly degenerated blood clot separated from the ovarian tissue by a layer of hyaline material. Fig. 2 is a magnification of the blocked area in Fig. 1. On the right center edge is a well-preserved chorionic villus without any recognizable vessels but surrounded by a thin layer of syncytium and with a collection of syncytial cells on one side. At the extreme left, opposite this villus, many decidual cells are seen in the wall at the site of implantation. There was no endometrial tissue in the sections examined.

Specimen from the left ovary consisted of a cyst membrane which microscopically revealed a cystic corpus luteum.

*Pathologic Diagnosis.*—Ruptured ectopic pregnancy, primary in the right ovary, and corpus luteum cyst of the left ovary.

## UNUSUAL COEXISTENCE OF GRANULOSA CELL TUMOR AND OVARIAN TERATOMA CONTAINING THYROID TISSUE\*

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**I**N GENERAL, 80 per cent of ovarian tumors are cystic and 20 per cent are solid (Dockerty). Dermoid cysts constitute about 10 per cent of the cystic tumors and are usually unilateral. The incidence of thyroid tissue found in dermoid cysts of the ovary varies from 1.5 per cent to 28.5 per cent, as cited by Wynne and his associates, quoting various authors. Probably a midground of about 10 per cent would be more correct. They also noted that the first strumal tumor of the ovary (ovarian tumor of thyroid tissue) was described by Gottschalk in 1899 under the name of "folliculoma malignum ovarii." According to the same authors a tumor of similar structure was recognized as containing thyroid tissue by Pick in 1902. Strumal tumors are most common among women more than forty years of age, may be cystic or solid, and usually cause symptoms referable to mechanical influence alone. Witherspoon stated that of the 50 recorded cases reviewed by him, in only 11 was the tumor composed entirely of thyroid tissue and in only two of these was it associated with goiter. Kovács observed the subsidence of definite symptoms of exophthalmic goiter after removal of a strumal tumor of the ovary. Trapl suggested that strumal tumors of the ovary may function vicariously as thyroid. Masson and Mueller reported 6 cases of ovarian tumors of thyroid tissue, in 3 of which they determined the iodine content. They found the iodine content in their Cases 1, 3, and 4 to be 0.105, 0.031, and 0.011 per cent dry weight, respectively. These authors stated that Ordtmann estimated the iodine content of the thyroid gland at approximately 0.1 per cent.

Of the solid ovarian tumors, the granulosa cell type constitutes 10 per cent. According to Te Linde, these tumors are responsible for about 1.1 per cent of postmenopausal bleeding. It is important to note that bleeding caused by this tumor is periodic and may be clinically indistinguishable from menstruation (Novak). This adds much weight to the thesis that periodic bleeding can occur in the absence of ovulation, for the stimulus afforded by the cells of the granulosa cell tumor is not associated with ovulation. Of other conditions causing postmenopausal bleeding, malignant lesions are responsible for about 60 per cent and benign lesions for about 40 per cent. The most common cause of postmenopausal bleeding is carcinoma of the cervix (37 per cent) with carcinoma of the fundus second (15 per cent). Prolapse with ulceration of the cervix accounts for 11 per cent, cervical polyp for 6 per cent, and endometrial polyp for 4 per cent. No other single condition accounts for more than 5 per cent of the remainder, according to the figures of Te Linde, in a survey of 179 cases of postmenopausal bleeding.

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311 COMMONWEALTH AVENUE

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**Cruickshank, Robert:** Bacteriology of Impetigo Contagiosa, Lancet 2: 275, 1941.

A bacteriologic study of 23 adult cases of impetigo revealed hemolytic streptococci of Lancefield Group A in 15 cases. In most instances the streptococcus was the predominant organism. Five of the 15 showed hemolytic streptococci in throat cultures. *Staphylococcus aureus* was found in 18 of the 23 skin lesions and was present in the 8 cases that failed to yield hemolytic streptococci. The staphylococcus was regarded, rightly or wrongly, as a secondary invader.

The author also points out that in Denmark an epidemic curve for impetigo with its peak in late autumn has been described. In England a minimal incidence is described in summer followed by a rapid rise in early autumn with the peak in November, a slight drop in December, and another rise to a maximum in January. This curve parallels but antedates by three to four weeks the incidence curve of scarlet fever.

CARL P. HUBER.



and 90 diastolic, and pulse 84. Results of examination of the heart, lungs and abdomen were negative. Pelvic examination revealed a tumor the size of a grapefruit filling the right side of the pelvis and apparently attached to the uterus. The diagnosis was ovarian cyst (right) or a degenerating fibroid.



Fig. 2.—*a*, Cystic glandular hyperplasia of endometrium with some evidence of differentiation as shown by coiling of the glands (hematoxylin and eosin  $\times 50$ ); *b*, granulosa cell tumor, cylindroid pattern, with transition to spindle-shaped theca cells. These theca cells contained lipoid as demonstrated by appropriate stains (hematoxylin and eosin  $\times 125$ ).

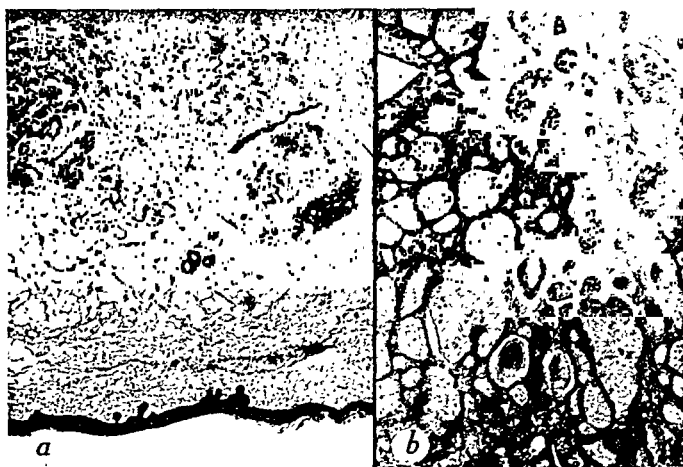


Fig. 3.—*a*, Dermoid (cystic teratoma); note skin, sweat glands, smooth muscle, adipose connective tissue and cartilage (hematoxylin and eosin  $\times 30$ ); *b*, the nodule of thyroid tissue. Most of the vesicles are well filled with colloid (hematoxylin and eosin  $\times 55$ ).

At operation on Nov. 8, 1941, a right ovarian cyst was found in addition to several small uterine fibroids. The uterus was slightly enlarged. Hysterectomy with bilateral salpingo-oophorectomy was performed.

*Pathologic Report.*—The specimen consisted of uterus, tubes, and ovaries. The uterus weighed 70 Gm. (normal weight 40 Gm.). The left ovary measured 2.5 by 2 by 2 cm. and was solid in consistency. Surfaces made by cutting were homogeneously grayish brown and somewhat fibrous. The right ovary measured 11 by 10 by 6 cm., weighed 455 Gm.,

## REPORT OF A CASE

A 56-year-old obese white woman first entered the Mayo Clinic on Aug. 4, 1926, for "an examination of her pelvis." Past medical history had been essentially negative. She had one child; there had been no other pregnancies. For sixteen years the patient had been experiencing symptoms of the menopause; her last menstrual period had occurred early in 1925. Eight years prior to admission she had experienced a severe episode of vaginal bleeding. The bleeding had ceased following "clipping" from the uterus of some tissue which, she had been assured, was not malignant.

Examination here on Aug. 4, 1926, disclosed a cervical polyp; the uterus was enlarged two times normal size and the enlargement seemed to be more on the right side than on the left. The clinical diagnosis was cervical polyp and fibroid of the uterus or an ovarian cyst (the former more probable). Immediate operation was not insisted on but the patient was advised to have an examination every six months and to return for an operation if the mass gave trouble or increased in size.



Fig. 1.—The uterus is large for a senile organ. The other features are indicated by the arrows.

The patient returned to the clinic on Nov. 6, 1941. She stated that she had been well until July 17, 1941, at which time she had slight vaginal bleeding. Curettage was performed at that time with removal of a benign polyp. There was no further bleeding until Aug. 28, 1941, at which time, the patient said, she had experienced a profuse "period." Another curettage was performed and multiple benign polyps were found and removed. The physician also told her she had a tumor of the right ovary. Since this last operation, the patient had been suffering from a brownish watery discharge gradually diminishing in amount.

At examination on November 6, the patient appeared unusually well preserved for her age (looked ten to fifteen years younger). Her weight was 175 pounds (79 kg.), blood pressure 175 mm. of mercury systolic

## BILATERAL BRENNER TUMOR OF THE OVARY

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**A**LTHOUGH Brenner tumors are comparatively rare, still they are probably not as infrequent as the literature would have us believe. Up to 1938 Varangot<sup>1</sup> was able to collect 108 cases from the literature. Since that time several additional cases have been recorded; 1 by Eleizegui,<sup>2</sup> 10 by Docherty and MacCarty,<sup>3</sup> 2 by Walton,<sup>4</sup> 14 by Novak and Jones,<sup>5</sup> 10 by Smith and Pettit,<sup>6</sup> 9 by Timmerberg,<sup>7</sup> 1 by Lemgruber, MacClure and de Oliveira,<sup>8</sup> 1 by Chiray, Albot and Balmez,<sup>9</sup> 1 by Siegel<sup>10</sup> and 1 by Etcheverry and Martinez de Hoz<sup>11</sup> bringing the total to 159 (including this case). We feel that this case should be presented because of the unusual clinical history, the gross appearance of the specimen and because of the fact that we will be able to arrive at a true estimate of the incidence of these tumors only if all cases are reported.

In 1899 Orthman<sup>12</sup> described what we now consider the first case of Brenner tumor, followed in 1907 by Brenner's<sup>13</sup> three cases to which he gave the name "oophoroma folliculare," because he believed the source to be the follicle. However, since Meyer's<sup>14</sup> paper and explanation of their origin from Walthard<sup>15</sup> inclusions, these tumors have been more accurately classified and their histogenesis has been more clearly defined. Schiller<sup>16</sup> points out that in some instances these tumors may arise from Wolffian epoophoron tubules which are included in the ovarian hilum and which may form epithelium like that normally found in the urinary tract. However, most investigators favor the Walthard inclusion source.

The Brenner tumor is slow growing and considered a benign lesion. It is usually unilateral, although it may be bilateral. Over 50 per cent occur beyond the age of fifty years. It produces no hormonal disturbances of the endometrium and no characteristic symptoms so that it is usually found incidentally at operation or autopsy. The size varies between a few millimeters to several centimeters, the largest recorded being 15 pounds as reported by Neiman.<sup>17</sup> The tumor may assume a solid or cystic form. The former has much the appearance of a fibroma, the cut surface, however, presenting a yellowish tint. Necrosis and hemorrhage are rare findings. Two features are necessary for the microscopic diagnosis, namely the characteristic nests of epithelial cells, which resemble squamous cells, although they do not possess intercellular bridges or keratin and a fibrous connective tissue stroma surrounding the epithelial nests.

### CASE REPORT

L. M., a white female, married, age 50 years, was admitted to Temple University Hospital on April 1, 1941. Her chief complaints were stiff-

and was cystic. On section the cyst was seen to be filled with semisolid gelatinous, greasy material containing hair. In the wall was a semisolid translucent brownish nodule, 2.5 cm. in diameter, which on cut section grossly resembled normal thyroid. The uterus was large and contained numerous fibromyomas, ranging from 5 mm. to 2 cm. in diameter. The endometrium was 5 mm. in thickness and presented numerous polyps. The cervix was fibrotic and contained a few small cysts filled with gelatinous material. The Fallopian tubes presented chronic inflammatory changes (Fig. 1).

*Microscopic Examination.*—Multiple leiomyomas of the uterus, cystic hyperplasia of endometrium (Fig. 2, *a*) with polyps (benign), chronic cervicitis, bilateral chronic salpingitis, granulosa cell tumor of the left ovary showing transition to theca cell type (Fig. 2, *b*) (Dockerty), and dermoid cyst (benign teratoma) (Fig. 3, *a*) of the right ovary containing thyroid tissue were observed (Fig. 3, *b*). The latter showed Grade 2 (on basis of 1 to 4) parenchymatous hypertrophy (Fig. 4).



Fig. 4.—The region of "ovarian exophthalmic goiter." Note the tall epithelium, papillary infoldings and thin vacuolated colloid (hematoxylin and eosin  $\times 165$ ).

This case, in retrospect, illustrates the importance of suspecting granulosa cell tumor when any patient past the menopause presents herself because of periodic vaginal bleeding and especially when curettage from such a patient reveals endometrial hyperplasia. It also emphasizes the difficulty of distinguishing, clinically, uterine fibromyomas from ovarian cysts. Finally, from a purely pathologic viewpoint, the extremely rare coexistence of granulosa cell tumor and hyperplastic strumal tumor is of unusual interest. Search of the literature revealed only one other similar instance (Frankl).

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mucopurulent discharge. The uterus was normal in size, retrocessed and fixed a little to the right. A large tender mass was palpated in front of the uterus, occupying the whole of the left pelvis. This was interpreted as a large tuboovarian abscess. Operation was advised and performed on April 4, 1941, with the findings of bilateral ovarian fibromas. The right ovarian fibroma had two twists in its pedicle and was gangrenous. It had almost amputated its pedicle and was in the left pelvis anterior to the broad ligament. The left ovarian mass was free in the abdomen. A bilateral ovariectomy and partial salpingectomy was done and the specimen was sent to the laboratory.

The pathologic report (31129) stated that the specimen consisted of both ovaries and portions of both Fallopian tubes. One tube and ovary (right) was a large reddish black necrotic mass measuring 12 by 7 cm.



Fig. 2.—Photomicrograph showing the characteristic nests of epithelial cells in a dense fibrous supportive stroma.

Cut sections revealed a trabeculated, reddish black, hemorrhagic, moderately firm parenchyma. In the broad ligament there was a large vascular channel stuffed with blood. The opposite ovary measured 12 by 8 by 7 cm. It was well encapsulated and smooth. The outer surface was lobulated and the cut surfaces presented a white, firm, trabeculated parenchyma, showing scattered areas of softer yellow tissue. The corresponding tube measured 7.5 cm. in length and was grossly normal.

Microscopic sections of the right ovarian mass revealed hemorrhagic necrosis, but in some areas the architecture was well preserved and here were seen nests of epithelial cells embedded in a dense fibrous stroma. The opposite ovary revealed the typical picture of a Brenner tumor showing an occasional area of cyst formation and calcification.

The patient made an uneventful recovery and was discharged on April 21, 1941, much improved with the diagnosis of rheumatoid arthritis, bilateral Brenner tumor, and food allergy.

This case clearly illustrates the apparent silent behavior of a Brenner tumor. Prior to the patient's discharge a curettage of the uterus was done. The fragments, however, were insufficient for a satisfactory histologic diagnosis. They showed only a few glands and a dense stroma.

ness and swelling of the joints following an attack of "la grippe" in December, 1940.

Systemic inquiry revealed nothing further of significance. Her menses began at an early age and were regular until Dec. 10, 1940. Since then she has had no periods or bleeding and has had no menopausal symptoms.

Physical examination revealed a well-developed and well-nourished adult female. There was enlargement of the isthmus and of the left lobe of the thyroid. Heart and lungs were normal. The abdomen was not tender. The liver and spleen were not palpable, but in the midline



Fig. 1.—Gross specimen of the ovarian tumors. Hemorrhagic necrosis of the right ovarian mass (upper part of photo) is clearly visible.

and slightly toward the right side there was a firm mass which disappeared as it was followed into the pelvis. This apparently represented an enlarged fibroid uterus. The extremities revealed swelling, stiffness, and limitation of the knee and ankle joints with some swelling of both wrists and of the interphalangeal joints of the right middle and index fingers.

On admission, temperature, pulse, and respirations were normal, but on the three following days the temperature rose gradually to 99.8° F. Basal metabolic rate was +30.

Pelvic examination on the day following admission revealed the vulva and vagina to be negative. The cervix was normal except for a profuse

All her children were living and well. Both parents were dead of unknown causes. Her husband is at present confined to a mental institution. There is no family history of diabetes, tuberculosis or cancer.

Physical examination revealed a well-nourished female, with a slight tendency to adiposity, who did not appear either acutely or chronically ill. She presented essentially negative objective physical findings except for those noted upon bimanual and vaginal examination. These findings were practically identical with those noted upon her four previous hospital admissions, and consisted essentially of a slightly enlarged uterus, regular in outline, lying in third degree retroversion, and moved forward with great difficulty. The cervix upon inspection again revealed, for the fifth time, the presence of several succulent polyps extruding through the external os. Upon her four previous admissions, she had had a simple polypectomy and uterine curettage; a wide cervical excision, polypectomy, and cauterization upon two occasions; and, upon her last previous admission, a high cervical amputation. Pathologic reports upon all the tissues obtained had signified the presence of benign polyps, although, upon one occasion, the pathologist had expressed a verbal opinion of a suspected malignancy.

The blood pressure was 120/74; urine, negative; Wassermann and Kahn tests, negative. Blood sugar was 80, and urea nitrogen 14. Vaginal, cervical, and urethral smears were negative for gram-negative intracellular diplococci. Blood examination showed hemoglobin 12 Gm.; red blood count, 3,060,000; white blood count, 11,000 with polymorphonuclears 79, eosinophiles 2, and lymphocytes 19.

In view of the patient's age, constantly recurring polyps with bleeding, and a suspected malignancy, it was deemed advisable, at this time, to advocate a total abdominal hysterectomy. Under spinal anesthesia, this was performed on Nov. 28, 1941, with the following findings: The uterus was slightly enlarged, nonadherent and regular except for the presence of a small pedunculated fibroid on its anterior surface. The adnexa were grossly normal. There were no visceral or peritoneal implantations. The cervix was hypertrophied, short, and stumpy, with several grapelike polyps extruding through the external os. There were no glandular enlargements.

*Pathologic Report.*—(Lab. No. 11956—Dr. A. R. Kantrowitz.) *Gross:* Specimen consisted of a completely resected uterus, together with the cervix, measuring 10 by 7 by 5 cm. A pedunculated mass, 1.8 cm. in diameter, was adherent to the anterior wall immediately inferior to the right round ligament. Numerous hemorrhagic polypoid excrescences, ranging up to 0.9 cm. in diameter, projected in grapelike clusters through the external os. The right and left tubes and ovaries were removed together with the uterus. The uterus was opened along the posterior wall. The projecting mass measured 3 cm. in length and up to 1.7 cm. in diameter. It was found to arise from the anterior wall of the cervix. Upon opening into the endometrial cavity, the cavity was found to measure 8.5 cm. in length. The endometrium presented a succulent appearance. When the polypoid mass was raised, the anterior wall was found to present an angry red, finely granular appearance with considerable mucoid secretion, providing a glistening surface. An area of pearly gray thickening was noted on the endometrium at the internal os.

## SUMMARY

An unusual case of bilateral Brenner tumor in a 50-year-old female is reported. It was complicated by strangulation of the right ovarian mass through torsion of the pedicle.

We are indebted to Dr. H. A. Duncan, Clinical Professor of Gynecology, Temple University Medical School and Hospital, for permission to report this case along with his clinical observations.

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## SARCOMA BOTRYOIDES OF THE CERVIX

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**B**ECAUSE of the rarity of occurrence of mixed mesodermal tumors of the cervix, the following case report is herewith submitted:

S. G. (No. 100,348), aged 45 years, white, Russian Jewess, was admitted to the Beth Moses Hospital on Nov. 23, 1941. This was her fifth admission in a period of thirteen months, at about three- to four-month intervals, and always with the same complaint of irregular vaginal bleeding.

Her menstrual cycle which began at the age of 12, at twenty-eight-day intervals and lasting for six days, had always been of a normal rhythm up to the time of her first admission to the hospital on Oct. 14, 1940. At this time, she had complained of a menometrorrhagia of four months' duration.

Except for the usual diseases of childhood, there was no history of any previous illness. There were no previous operations except for those performed upon her four previous hospital admissions noted above.

She had been married 28 years, and was a gravida viii and para vii, had had one induced abortion and no history of any obstetric difficulties.



myometrium. The cervical polyps consisted of granulation tissue with mononuclear and polynuclear cells. Nests of spindle and round cells were noted within the cervical stroma. In areas the nests presented the appearance of embryonal mesenchyme, with its stellate cells and loose intercellular substance. Considerable atypism and numerous mitoses were noted. In other areas considerable anaplasia was noted. Striated muscle fibers were also present.

*Diagnosis.*—Sarcoma botryoides of the cervix; localized adenomyosis uteri; corpus luteum (right ovary); early premenstrual endometrium.

Her postoperative course was uneventful except for the development, upon the sixth postoperative day, of a frequency, urgency, and incontinence of urination. Cystoscopy and biopsy of a small necrotic area in the base of the bladder failed to reveal the presence of any malignant tissue or the presence of a vesicovaginal fistula. Methylene blue instilled into the bladder did not appear in the vagina.

She was discharged in good condition on Dec. 28, 1941, and was referred to the Brooklyn Cancer Institute where she is now receiving irradiation.

#### SUMMARY AND DISCUSSION

First reported in 1854, 94 cases of sarcoma botryoides of the uterus have been recorded in the literature. Of these, 36 have been confined to the cervix. Of a highly malignant nature, the average duration of life is one year after discovery despite all forms of treatment. Among the histologic elements noted are many which are foreign to the uterus, such as cartilage, striated muscle, myxomatous tissue, and sarcomatous stroma. It was primarily our intent, in submitting this report, to record another case of this rare and highly malignant form of uterine tumor. Our own case is especially characterized by its occurrence at an adult age, the presence of constantly recurring cervical polyps with irregular vaginal bleeding, and, in the microscopic picture, the presence of striated muscle. For a complete review of this subject, one need only to refer to the recent and comprehensive report by Glass and Goldsmith.<sup>1</sup>

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The anorectal type of case usually has a stricture though some cases do not. Abscesses, fistulas, and sinuses may be present around the anus. Peritonitis, liver abscess, renal involvement, and systemic manifestations of all kinds may be associated with this disease. The author's experience has been that the operative treatment of this condition must be undertaken in 2 stages. In the first step, a colostomy is done and all abscesses about the anus are drained. This is followed in three weeks by a mucosal stripping operation. The author feels that this same procedure could be used for cases of multiple fistulas.

WILLIAM BERMAN.

This resulted in a somewhat narrowed endometrial canal. Cross section through the cervix, through the middle of the anterior wall, revealed a pinkish red succulent mass, 1.2 cm. in diameter, deep within the cervical myometrium.

The right and left tubes measured 9 cm. in length, respectively. Their fimbriated ends were patent. The ovaries were of normal size and shape. The right contained an hemorrhagic lateral portion comprising one-third

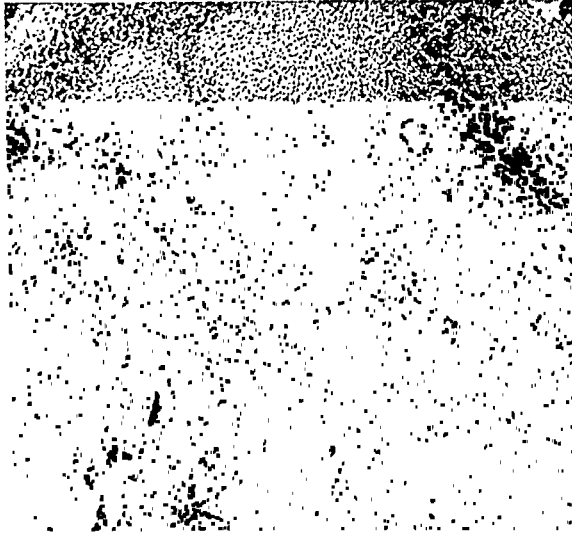


Fig. 1.—Sarcoma tissue in the cervix (low power).

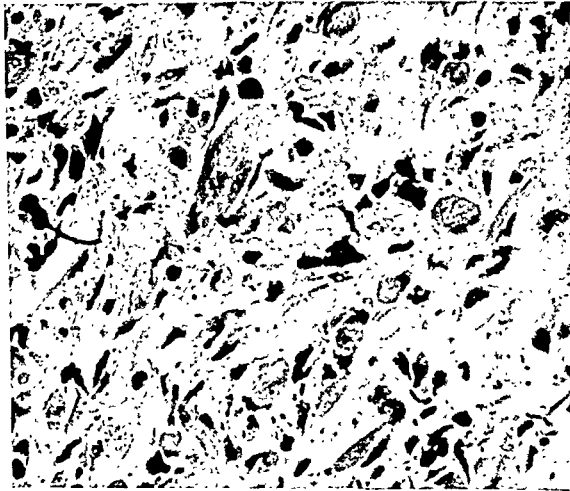


Fig. 2.—Striated muscle fibers in the cervical stroma (high power).

of the ovary. Cross section revealed a small, clot-filled cyst bordered by a golden yellow undulating membrane. The left ovary contained a similar cystic area in its mesial third. This was filled with clear serous fluid.

*Microscopic:* (Figs. 1 and 2.) The endometrium was in a very early secretory phase. Downgrowths of the endometrium were noted in the

never had a prolonged cough, hemoptysis, night sweats, or loss of weight. Roentgen ray examination of the chest was negative. She had had a supravaginal hysterectomy and bilateral salpingo-oophorectomy for leiomyomas of the uterus eighteen months before examination. At that time the vulva was examined and considered normal. At no time was there leucoplakia or pruritus vulvae. Both from history and physical examination there was no suggestion of tuberculosis in the patient's husband. Physical examination of the patient was negative except for a well-healed lower abdominal midline scar and an ulcerated area on the vulva. This involved the major and minor labia and the mucosa adjacent to the vulva. A presumptive diagnosis of carcinoma of the vulva was made.

A biopsy of the ulcerated area did not show malignant tissue. There was instead caseous necrosis with typical tuberculous inflammation and many giant cells. A second and third biopsy revealed identical microscopic structure (Fig. 1). A complete vulvectomy, including the clitoris and the terminal half inch of the urethra, was performed. The cut end of the urethra was approximated to the cut edges of the mucous membrane by interrupted silk sutures. No neoplastic tissues were found on examination of the entire specimen. Convalescence was uneventful, and the patient left the hospital on the thirteenth postoperative day. Two months later a silk suture was removed from granulation tissue around the urethra. Two months after this, persistent granulation tissue was treated by electrodesiccation. The patient is now free from discomfort two and one-half years after operation. Intercourse is possible without pain. On examination there is no ulceration and the tissues are well healed. There has been no inguinal adenopathy at any time.

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In the period between 1912 and 1941, 4,532 mammary lesions were seen at the Portuguese Institute of Oncology; 1,862 were benign and 2,661 malignant. The greatest incidence of pathology was in the 40 to 50 age group. Most patients had initial symptoms at any time within 5 or 6 years, a scattered few having their first symptoms as much as 30 years before reporting for treatment. In 436 cases a swelling or tumor was the first thing noticed by the patient. Stinging sensations, enlargement of the breast were the next most common symptoms.

Trauma was a factor in 100 cases. Diagnosis of a lesion was made in 3 cases fifteen days after simple trauma, in 16 cases from 1 to 8 months after nonsurgical trauma and the remainder were well distributed from one to forty years subsequent to various surgical procedures. Applying strict criteria of relation of trauma to tumor, the author concludes that this relation could not be proved in the majority of cases of the group under study, although in some cases carcinomatous changes appear to have occurred in postoperative cicatricial tissue or in an organized hematoma. The right breast was involved in 302, the left in 313, both in 10 cases of the group. The upper external quadrant was the most common location, seconded in incidence by total involvement. The author presents an excellent and extensive statistical study of treatment, histology, and family histories of carcinoma.

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## TUBERCULOSIS OF THE VULVA

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**T**UBERCULOSIS of the vulva is uncommon enough to be considered a medical curiosity. In the foreign literature it has been reported at infrequent intervals but in certain of these instances doubt arises as to whether the patient had lymphogranuloma inguinale or tuberculosis of the vulva. In the American literature reports of patients with tuberculosis of the vulva are exceedingly rare (last report 1935). The signs, symptoms, and gross appearance of tuberculosis of the vulva may be almost identical to those of carcinoma of the vulva and herein lies its chief importance for the two are easily confused. Such confusion is



Fig. 1.

unfortunate since simple vulvectomy is usually sufficient to cure the patient with tuberculosis of the vulva, but when carcinoma is present, a groin dissection of the Basset type is indicated. The addition of groin dissection to vulvectomy greatly increases the morbidity and mortality and would be an unfortunate mistake should the patient have tuberculosis rather than cancer of the vulva. A short case report of a patient with tuberculosis of the vulva is here appended:

C. R., aged 44 years, white, married, nulliparous, complained of intense pain and burning in the vulva of eight months' duration. This was associated with an ulceration of the labia which had increased in size progressively. Discomfort was aggravated by micturition. The patient had

Basically, its main working part is a reciprocating, tapered valve which slides gently to and fro past openings through which oxygen (or other gas) flows to and from the lungs. This valve is moved by a gas motor operated by the same source of compressed gas or gas mixture

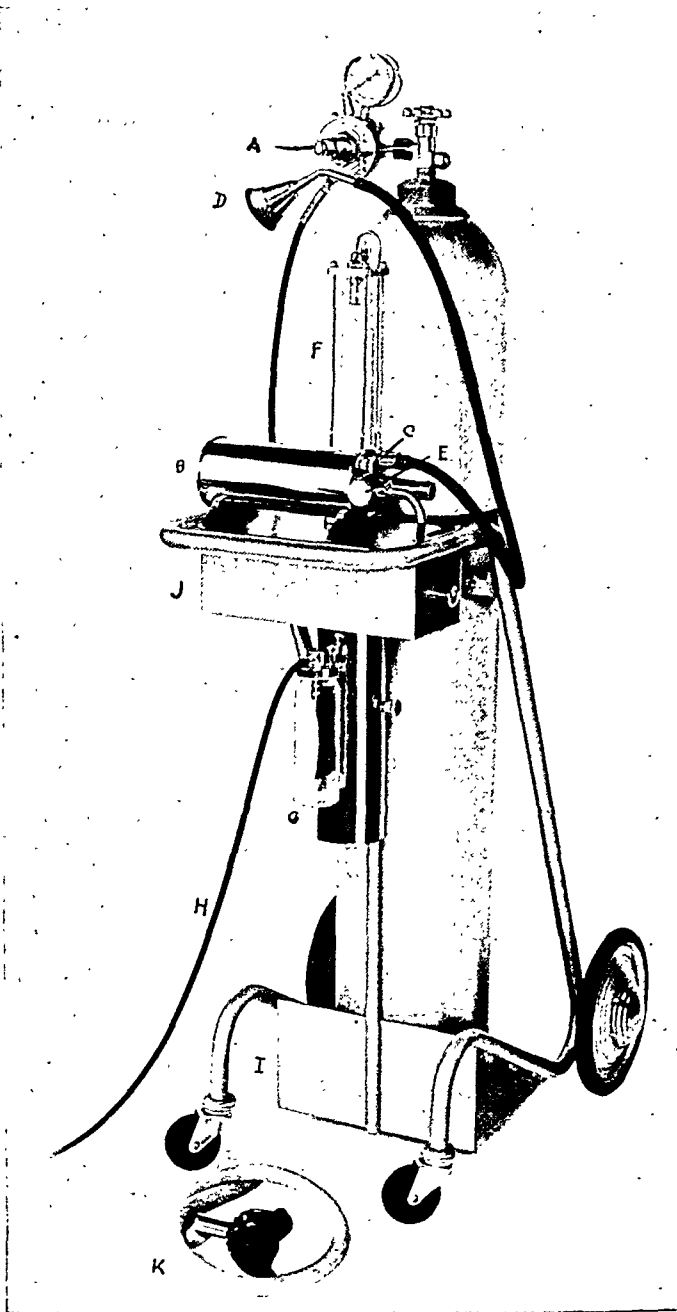


Fig. 1.

that flows to the patient. The rate of pulsation and the volume of each respiration are controlled independently. The operator need not be concerned about pressure—this adjusts itself automatically to the volume of inflow, which is adjusted in each instance to the capacity of

# AN APPARATUS FOR RESUSCITATION OF NEWBORN INFANTS

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**A**UTHORITIES<sup>1, 2</sup> are now agreed that the treatment of asphyxia neonatorum should consist of proper posture, body warmth, removal of any substance obstructing the upper respiratory passages, and finally the administration of 100 per cent oxygen by a simple, effective and comparatively foolproof mechanism.

Posture and warmth can be managed so readily in all hospital delivery rooms that nothing additional need be added in that regard.

Aspiration and resuscitation methods have been varied and manifold. It is not in the province of this paper to review these methods other than to say that with the replacement of manual methods by mechanical devices, simplification has been sought in order to obviate mechanical failure, and to improve efficiency. The one phase of the subject with which this paper deals is the presentation of a simple mechanical device for the purpose of administering 100 per cent oxygen to a newborn infant after first having thoroughly cleansed the air passages of obstructive material by means of an aspirator attached to the device.

It is true that asphyxia neonatorum is best treated by preventing it.<sup>3</sup> With prophylaxis in its present state, and with analgesia in widespread use, any consecutive series of births will indicate that approximately 15 per cent of the newborn infants show some degree of asphyxia ranging from a mild pallor to cyanosis.

The primary requisite of the ideal resuscitator is that it should be able to simulate natural respiration in volume and in rhythm. The flow should begin and end gently as it does in normal breathing. The device should be adaptable for use on a human being of any age, size, or physical condition. It should be automatic and thus, once adjusted, not susceptible to the whims of the operator. The controls should be few, simple, and easily learned. The resuscitator should be safe, efficient and reliable and should be widely adaptable for use with any gas or gas mixture necessary for resuscitation.

The authors were appointed a committee by the departments of obstetrics and gynecology at Mount Sinai Hospital in 1939 for the purpose of investigating and recommending a resuscitator for use in the delivery suite. Four resuscitators were investigated and subsequently obtained for trial use for from thirty to ninety days. The relative merits of these machines need not be discussed here. Our investigation, together with the unanimous opinion of the staff indicated that the Dann resuscitator was best fitted for our requirements. It is now close to two years during which time this resuscitator has been in constant use. In view of the fact that this machine has never been described, it is being presented herewith and shown in Fig. 1.

moved alongside the mother. A sterile glass tube and rubber catheter is available for attachment to the aspirator tubing (*H*). The obstetrician is then handed the catheter already attached to the tubing by a nurse who, at the same time, sets the aspirator in motion. The obstetrician then can aspirate the nose, mouth, and pharynx before completing delivery of the infant. This aspirator has also been used successfully on several mothers, with the recovery of aspirated vomitus from the upper respiratory tract, and with the avoidance of severe complications.

As will be noted in Fig. 1, the resuscitator is attached to a mobile steel cart (*I*) which rolls noiselessly. This cart holds a large oxygen cylinder and occupies a floor space of 20 by 30 inches. It has a drawer space (*J*) for face masks, intubator, and other accessories (adult mask [*K*]).

As previously mentioned, the increasing use of analgesia and anesthesia in parturient mothers has made fetal asphyxia a more common occurrence. Various measures have been employed to initiate respiration in the newborn infant, both manual and mechanical, but none have been so simple, rapid and effective as the gentle pulsating flow of this resuscitator. A particular advantage of this respirator is its ability to expand the atelectatic lung of the newborn infant. Machines in which the pressure only is controlled are often incapable to initial filling of the lungs because this requires greater pressure (owing to the adhesion of the lung surfaces) than subsequent inflations. In this resuscitator the volume is adjusted to the needs of the infant and this, once adjusted, can never exceed the capacity of the lungs. At the same time the machine, when this is necessary, automatically permits enough pressure to be built up to overcome the adhesion of the lung tissues. Thus, once the rate is set, the operator need only adjust the machine for proper expansion of the lung. Spontaneous respiration in the infant usually occurs within a few minutes, often in a few seconds.

This resuscitator is so simple in its operation that the entire obstetric and nursing staff have been trained in its use in a very short time. The only essential knowledge needed to operate the apparatus is a practical understanding of the mechanism of respiration. We feel that any individual who understands the fundamentals of respiration and who has learned how to adjust the two control knobs on the machine can give artificial respiration to the newborn infant with complete safety.

#### SUMMARY

1. The Dann resuscitator is a safe, efficient, positive pressure respirator.

2. It is simple and virtually foolproof in design, having only two controls.

3. The rate and volume of respiration are independently adjusted to the physiologic needs of the infant.

4. Once adjusted the machine is entirely automatic. Its rhythmic, gentle insufflations simulate natural respiration. Exhalation occurs spontaneously.

5. The attached aspirator may be used before full delivery of the infant and should always be used before starting resuscitation. In use, it may be readily alternated with the resuscitator.

6. The simplicity of this machine makes it easily operated by almost anyone.

the lungs. Exhalation is completely spontaneous; the lungs empty themselves as they do in normal breathing, by the elasticity of the thoracic cage and of the lungs themselves.

Oxygen is supplied to the resuscitator from a cylinder through a pressure reducing valve (*A*), set to the proper pressure at which the machine is designed to operate. A very small portion of the gas passes to the air motor (*B*). The rate control valve (*C*) controls the flow of this portion of the gas and thus increases or decreases the rhythm of the motor. By means of this valve, the rate is first adjusted to the needs of the patient (from 20 to 25 per minute for infants). Then applying the face mask (*D*) to the infant, the volume control valve (*E*) is slowly opened until proper chest expansion takes place. No further adjustment is necessary. This valve permits oxygen to flow from the pressure-reducing device on the cylinder past a tapered reciprocating piston, through an expansion chamber to the patient. At the end of each inflow, the piston automatically cuts off the flow of oxygen and opens a port in the machine to the outside air which permits free exhalation, without suction of any kind. The piston then closes this port and gently opens another, through which oxygen again flows to the infant.

The simple mechanism of this resuscitator has been so designed that even in newborn infants no delicate manometer has been found necessary to indicate the actual pressure of the oxygen mixture in the lungs. So long as the volume control valve is opened slowly and precisely to the point at which chest expansion occurs (a point easily observed), there is no danger of reaching excessive pressure in the lungs, even in premature infants. The controls on the resuscitator permit the flow to be adjusted exactly to the physiologic needs of the infant. Except for the indicators on the oxygen cylinder, gauges have purposely been omitted from this machine. Our experience with other resuscitators left us with the impression that such gauges provided a false sense of security—because the operator tends to watch the gauge or meter and not the infant. In addition, gauges and flow meters do not account for small leaks which may occur about the face mask. With this resuscitator, the operator gives undivided attention to the patient, adjusting the controls to the response of the subject.

Some members of the staff felt that a manometer would be a helpful addition to the resuscitator. As a result, a sensitive water manometer (*F*) was designed and attached to this machine. It indicates pressures up to 22 cm. of water (16 mm. of mercury) and does not permit the pressure to exceed this level. Through a small valve the manometer may be used or excluded as the operator desires. It is important to remember that it may be necessary for the initial pressure to exceed 22 cm. of water to inflate an atelectatic lung. Once the alveoli are opened, insufflation of the same amount of air will usually give pressures below 15 cm.

Attached to the resuscitator is a special aspirator (*G*). This also operates from the gas cylinder and provides rapid, rhythmic suction which may be varied by the operator from one to 160 cm. of water for preliminary removal of mucous or other material that may block the air passages and prevent ingress of the resuscitating gas. Together with a suitable collecting bottle, this aspirator is admirably adapted for use in the delivery room, in that it can be used as soon as the baby's head is delivered. When so used, the entire resuscitator, which is mobile, is



making it more easily possible to unify one's data for purposes of comparison, when this is justified.

The basis of the method is that every normal cycle is considered to have a duration of 100 per cent, and any given day thereof represents a specific percentile of the whole. This is exemplified at the top of Fig. 1.

To use this nomogram, two facts and three procedures are required. One must know first, the number of days in a given menstrual cycle and, second, the number of days before the onset of the next menstrual period that a given event, or procedure, in the menstrual history occurs. With these facts, one looks (a) at the bottom legend for the specific day before the onset of menstruation; (b), at the left, for the number of days which that cycle lasted, and (c) one follows the abscissa, from the left, to the point of intersection with the curved line for the desired day, and from the *corresponding vertical ordinate, at the top*, the percentage value of the cycle is obtained.

Two examples of the use of this procedure are as follows: (A) An observation made on the sixteenth day before the onset of menstruation (read at bottom) of a thirty-two-day cycle (read at left), is at the 50 per cent point (read at top) of the cycle, directly above the indicated point of intersection of the three lines. (B) The sixteenth day before menstruation (read at bottom), of a cycle twenty-two days in length (read at left) is at the 27 to 28 per cent point (read at top) of the menstrual cycle. Similarly one may read the position of any other day, or fraction thereof, if one chooses to read that closely.

By use of a similar type of nomogram, one might equally well compare data from periods of gestation of differing lengths within a given species, and possibly between several species.

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**Loeser, Alfred A.: Mammary Carcinoma, Response to Implantation of Male Hormone and Progesterone, Lancet 2: 698, 1941.**

On the assumption that excess of estrogenic substance is a factor in producing cancer of the breast, an attempt was made to counteract this effect by implanting male hormone.

In mice of a strain showing a very high incidence of breast cancer, testosterone propionate was implanted subcutaneously in 10 every three to five weeks while 12 acted as controls. Implantation was not begun until the mice had had three litters. In the treated group 4 and in the control group 9 died of cancer.

In 6 women with a family history of breast cancer who had had their breasts amputated for carcinoma, testosterone propionate or progesterone or both were repeatedly implanted and in 2 progesterone was also given by mouth. In 3, recurrences were present at the time of implantation, and though 2 of these improved temporarily in general health, the progress of the cancer was not checked. In 3 no recurrences or metastases were present at the time of implantation, and none has appeared in the subsequent five years.

It is suggested that male hormone should be implanted in the operation site when the breast is removed for carcinoma, and implantation should be repeated when signs of masculinization disappear.

CARL P. HUBER.

We are indebted to Mr. Morris Dann (735 Thornhill Drive, Cleveland, O.), designer and manufacturer of this resuscitator for his technical cooperation, and to Dr. M. S. Biskind of New York City for his editorial assistance in the preparation of this manuscript.

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## METHOD FOR CORRELATING DATA FROM MENSTRUAL CYCLES OF DIFFERENT LENGTHS

### A SIMPLE NOMOGRAPHIC PROCEDURE

SAMUEL R. M. REYNOLDS, PH.D., BALTIMORE, MD.

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IN CLINICAL and laboratory investigations of the menstrual cycle, one is confronted with the problem of bringing together data from cycles, which though normal in every respect, differ greatly from each other in length. Thus, an observation made on the fifth day of a cycle of twenty-four days in total length may not be compared, on the basis of

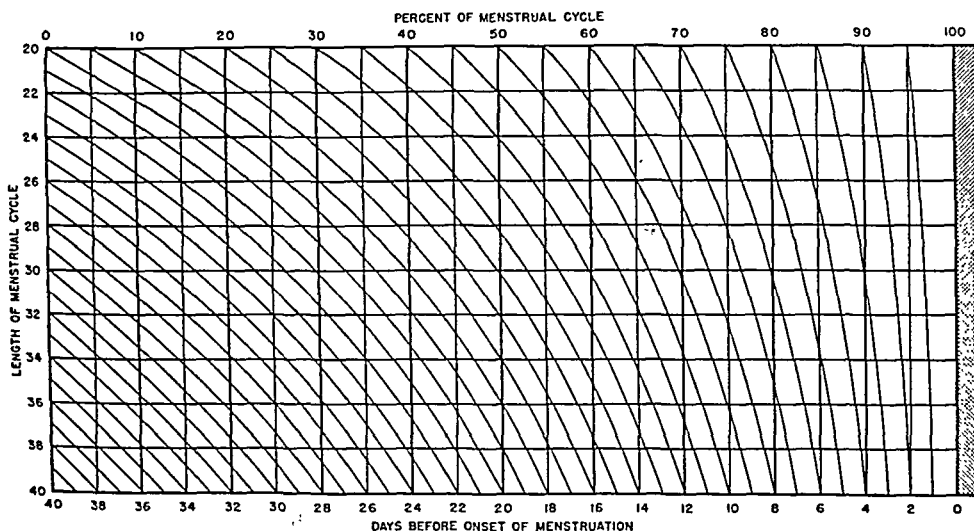


Fig. 1.—Nomogram for determining the percentile value of any day of a menstrual cycle, counting back from the onset of the next menstrual period. To be used for cycles twenty to forty days in duration. See text for description and use of this device.

any known sequence of physiologic events, with observations made on the fifth day of a cycle thirty-four days in length. One is tempted to arbitrarily disregard cycles outside a given range of duration, or to try to discuss a group of miscellaneous data on the basis of a figurative twenty-eight-day cycle. The simple device proposed in this note is no less empirical than the foregoing methods, but it possesses the merit of

The hemicelluloses of *Plantago ovata* and karaya gum both have the capacity of absorbing several times their volume of moisture and are valuable demulcents.<sup>1</sup> Karaya gum may be omitted in allergic individuals, the proportion of more extensive *Plantago ovata* being doubled.

The powder is applied by means of any powder blower, preferably with the patient in the knee-chest position, after the vagina has been dried with cotton pledgets. The patient is instructed to take a saline douche under pressure sufficient to distend the vagina just before her return to the office at the end of twenty-four to seventy-two hours. Such a douche will easily remove all the material. In the case of the inept woman who either cannot or will not take a douche properly, it



Fig. 1.—X-ray of pelvis of nullipara forty-eight hours after insufflation with "Tamplast," containing 20 per cent barium sulfate.

is well for the physician to assure himself that the material will be removed. A patient may also neglect to take her final douche after dismissal if she feels that she is already cured.

If douching is omitted, the vagina will be found to contain a soft, plastic mass which adheres gently to, but may be easily removed from, the surfaces of the cavity. If carefully removed en masse, it will be found to present the shape of the partially distended vagina, showing many of the rugae, etc. The pH of the surface of this cast will usually average 4.5, even though the vaginal pH at the beginning of treatment were considerably higher. The vaginal walls and portio will be found to be almost dry and of healthy appearance. There is virtually no odor to the mass removed as late as seventy-two hours even in cases of trichomonas vaginitis.

# AN IMPROVED VEHICLE FOR MEDICATION OF THE VAGINA

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School of Medicine)

ORDINARILY the efficacy of a therapeutic agent is roughly proportional to the efficiency with which it is applied. For skin diseases the dermatologist has a wide range of lotions, ointments, powders, wet compresses, etc., which keep the active agent in contact with the lesion for long periods of time. However, for treating affections of the vagina, lined with stratified squamous epithelium somewhat resembling skin, we have heretofore been limited to the use of douches, injections, tablets, and suppositories which are quite transient in their contact with the vaginal lesion. Tampons are used to treat the cervix, but their effect on the vaginal mucosa is one of prompt irritation, and they soon become malodorous. In recent years, insufflation of powders into the vagina has achieved considerable popularity, and this report deals with an attempt to improve such methods.

It seems logical to assume that a satisfactory vehicle for applying medication to the vagina should fulfill at least the following requirements:

1. It should be harmless to the patient.
2. It should be demulcent and antipruritic.
3. It should not soil or damage clothing.
4. It should be inexpensive.
5. It should be easy to apply.
6. The patient, herself, should be able to remove it.
7. It should remain in situ without the aid of tampons, pads, or cups.
8. It should gently maintain separation of the walls and folds of the cavity.
9. It should remain in contact with all surfaces for a prolonged period of time.
10. It should absorb secretions and discharges.
11. It should adsorb all odors.
12. It should provide a pH which is optimum and should maintain this pH for a prolonged period of time.
13. It should provide a medium for the growth of the normal vaginal flora.

Such a vehicle, for which the descriptive term "Tamplast"\* is suggested, has given satisfaction in my office practice for more than three years. It is composed of lactose, citric acid, finely divided kaolin, finely powdered hemicellulose of *Plantago ovata* and the exudative gum of *Anogeissus latifolia*. The finished product is a finely divided, whitish gray-colored powder of almost fluffy consistency with little or no distinguishable odor. This powder, when mixed with sufficient water to make a tenacious gum, has a pH of 4.0 to 4.5 due to its citric acid content. The lactose serves as a medium for growth of normal vaginal flora. Finely divided kaolin is one of our best adsorbents for odors.

\*Prepared by Marshall and Bell, Atlanta, Ga.

## Special Articles

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### CONTRIBUTIONS OF STUDIES ON PRIMATE ANIMALS

#### TO GYNECOLOGIC THOUGHT\*

CARL G. HARTMAN, PH.D., URBANA, ILL.

(From the University of Illinois)

IT MAY be presumptuous in me to attempt to diagnose gynecologic thought as of 1942 on the items I am going to discuss. I have found it profitable, however, to try to keep abreast the theoretical aspects of gynecology, partly through the literature but above all through my friends in the profession. It is certainly true that today clinician and laboratory experimenter are in close touch with each other. This is mutually beneficial, as has long been shown. The science of endocrinology owes its beginnings to the clinician, and clinical data continue to point to significant problems which animal experimentation aims to elucidate and thus to guide medical practice. It is my purpose to call attention to some contributions which apes and monkeys, particularly the rhesus monkey, have made to gynecology.

I realize further that, in a sense, I am bringing coal to Newcastle, speaking on this subject, since so many contributions to our topics have come from your laboratories. I need mention only Daron, Markee, Rossman, and others who worked with that master of the subject Bartelmez, who enjoyed the cooperation of clinicians like Culbertson and Brewer; Ivy, Rudolph and Danforth for their brilliant work on parturition, Klüver on behavior; Davis on vaginal reactions to hormones.

If one plots by year of publication, the literature list in Zuckermann's interesting little volume *Functional Affinities of Man, Monkeys and Apes* (1933), he will be struck by the sudden upswing of the curve with the turn of the century, particularly in the last decade of the period covered. It appears, too, from Ruch's *Bibliographia Primatologia* that more papers have been published on primates in the last two decades than in all previous history.

The modern studies have continued the basic morphologic studies of the nineteenth century, neurology being the chief growing point in this field, though it must be added that, in the modern spirit, functional aspects have received prime emphasis. The physical anthropologist has gathered his data from detailed study of primate skeletons of all orders (A. Schultz) and from dissection of cadavers, in order to determine more definitely primate relationships. Studies in behavior (Yale Laboratories) served to lift the apes and monkeys above the run of lower mammals, while studies in sex behavior and other forms [social behavior, both under laboratory conditions (Ball, Yerkes) and in the field (Carpenter)] have added considerably to our knowledge of our nearest kin in the animal world. Reproductive processes, particularly menstruation, embryonic development (Heuser and Streeter) and

\*Presented at a meeting of the Chicago Gynecological Society, January 16, 1942.

The vehicle will remain in situ for as long as twenty-four to seventy-two hours without the aid of tampons, pads, etc., often even in women with markedly relaxed perineal support (Fig. 1). The material acts as a demulcent and antipruritic, giving almost instantaneous relief, extending over the entire period of its use. The powder can advantageously be blown over the urethra and vulva, the patient being instructed not to void for several hours. Discharges are entirely absorbed by the medium, giving the patient immediate and lasting relief from this annoyance. The fastidious woman is also grateful for the prompt disappearance of all odor due to its adsorption in the mass.

Various therapeutic agents such as diodoquin, silver picrate, quinine, vioform, and other protozoacides may be added to the vehicle by substituting one of these for portions of the lactose up to 10 per cent. Diodoquin, 5 per cent, and vioform, 5 per cent, have given satisfaction in the treatment of trichomonas vaginitis.

Absorption of the discharge enables one to use silver picrate and even gentian violet intravaginally without the objectionable soiling of the patient's clothing and bed linens.

I have had limited experience with the use of this medium in monilia vaginitis, but in such cases the citric acid should be replaced by an alkali, such as aluminum hydroxide, to elevate the pH to about 7.5 or 8.0, and the lactose should be omitted. The formula described by Minnich<sup>2</sup> (sodium perborate, sodium lauryl sulfonate, thymol and aromatics) in proportions up to 6 per cent has given excellent results. It has been used without harm in the last months of pregnancy, giving complete relief from symptoms even when clinical cure was not obtained.

No ill effects have been observed from the use of this medium, either acid or alkaline, in a large number of cases. It probably should not be used in the presence of acute cervicitis of any kind, but it has been used to check the irritation of the vagina from chronic cervicitis and occasionally after separation of the slough of the cauterized cervix. In the experimental stage, one patient was insufflated with diodoquin in the acid medium once weekly for three weeks. No douches were used, the cast being removed instrumentally at the end of each seven-day period. The surfaces of these casts all presented a pH of 4.0 to 4.5 when removed, and there was no distinguishable odor. A vaginal smear taken when the last cast was removed at the beginning of the subsequent menstrual period was perfectly normal.

It is my impression that with the use of this vehicle the dosage of a therapeutic agent can be reduced and at the same time the number of treatments decreased, which together with longer intervals between treatments is of considerable economic importance. In the case of medications such as the estrogens, the powdered estrogenic substance may be insufflated into the distended vagina in the knee-chest position and the vehicle then blown into the cavity. This results in a plastic cast coated with estrogenic substance which remains in contact with all surfaces of the vagina for a prolonged period of time, greatly enhancing the local effect on the epithelium, hastening the appearance of the typical estrogenic reaction, and substantially reducing the cost of treatment.

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words, is delayed in the longer cycles, accurate records of the menstrual behavior of the patient become all the more necessary.

I think you will agree, therefore, that the former conception of regularity in menstrual schedule is a relative and not an absolute concept.

#### THE PRIMATE UTERUS

Fortunately, the menstruating organ, the uterus, is similar in structure in the higher monkeys, apes, and man, and this generalization applies to all of the details so far studied. It is possible to check many items and make direct comparison between the human tissues and those of monkeys. But the latter still offer the advantage of availability for biopsy and autopsy at the experimenter's will. There is the added advantage in the use of the monkey that it is possible to make vascular injections in a manner that can never be done in the human being and thus to learn vascular patterns in important structures.

One outcome of the monkey studies now in progress as a cooperative effort of Corner, Bartelmez, and myself will be the determination of exact time relations in the transformation of the endometrium after ovulation. Is the response variable or is the endometrium at twelve days after ovulation the same in all cases? We may state that a score of specimens of this period where the exact day of ovulation is known show great similarity in their histologic picture.

#### HORMONAL CONTROL OF MENSTRUATION

In response to ovarian hormones, the uteri of monkey, ape, and man are likewise similar. The monkey has, for that reason, proved invaluable in the search for the cause of menstruation. This problem is far from solution, although some of us have from time to time, in misplaced enthusiasm, felt that we were pretty close to the goal.

The gonadal hormones were first exploited, then extragonadal factors were invoked: anterior pituitary, posterior pituitary, the adrenal cortex, the adrenal medulla.

Beginning with E. Allen's classical experiments on the production of uterine bleeding in castrates that had received estrin, the search was on. We now know that the normal "Hitschmann and Adler" picture of the uterine cycle may be reproduced by estrogens accompanied, as in the normal cycle, by progesterone. Bleeding, moreover, follows soon after the cessation of treatment, just as after the removal of an active corpus luteum.

All these facts fitted in beautifully with the basic events of the menstrual cycle. But it was soon found that one could inhibit the bleeding with testosterone as also with desoxycorticosterone. Bleeding followed cessation of action of these hormones. Finally these hormones were found to stimulate growth of the endometrium, as indeed will progesterone alone, without priming with estrogen.

Perhaps it is an academic question, but it is often raised: which is the dominant hormone in the menstrual cycle, estrone or progesterone? Since nonovulatory cycles are indistinguishable outwardly from ovulatory ones or in the behavior of the blood vessels in intraocular transplants (Markee), progesterone is superfluous, unless, indeed, atretic follicles do produce progesterone. The problem is further complicated by the fact that in the ovulatory cycle, in the presence of an active corpus

placentation (Wislocki and Streeter) have been of special value to the clinician, as will appear below.

On the basis of all of these data it is apparent that seriation of the apes and monkeys on the basis of similarity to man depends on the character chosen: hand, foot, skull, pelvis, or the scores of indices the physical anthropologist has invented. Man is "primitive" with regard to one character, highly specialized with regard to another. On the whole, however, adding up scores, we must conclude, first, that the primates stand out from all other mammals and, second, that by and large the great apes or anthropoids (chimpanzee, gorilla, or orangutan) are more like man than the monkeys, the much studied chimpanzee perhaps the nearest to man of all of them. In this lecture some items will be mentioned substantiating this generalization.

That apes and monkeys menstruate at approximately the same intervals as women was first demonstrated by Cuvier in 1825. Since the publication of Corner's study of laboratory-kept rhesus monkeys exactly a century later, it has become apparent that the process is identical in monkeys, apes, and man. In this lecture I aim to touch on some of the high points of the physiology of the reproductive process of primates and with greater emphasis on my own researches perhaps than these deserve.

#### LENGTH OF MENSTRUAL CYCLE

Up to very recent years, the gynecologic world adhered to the idea that the "normal" woman menstruates at regular intervals of a lunar month. This insistence had its origin in the superstition of lunar control of the cycle, which even so objective a scientist as Arrhenius tried to substantiate. It is true that the average of numerous cycles of both the rhesus female and of women figures out to twenty-eight days. But here the "lunar influences" cease; the chimpanzee menstruates at intervals of about thirty-five days, while the estrous cycle of animals is of various lengths: four to five days in the mouse and rat; sixteen in the guinea pig; twenty-one in the pig, the cow, the mare; twice annually in the cat; and once annually in many wild forms. Moreover the first day of these cycles falls at random upon any given phase of the moon.

As soon as a sufficient number of female monkeys had been studied in various laboratories (the records of the Carnegie Colony now number thousands of cycles), with daily examination of the animals, it became apparent that no monkey female was absolutely regular, even the most fertile of them. Within the last decade it has become practically axiomatic in gynecologic circles that women, too, are far from "regular," and physicians now no longer take a woman's general impression based on all too faulty memory, of her "regularity" but are requiring calendar records of their patients. This is useful in itself, for from such records he can learn something, since very irregular periods may be associated with other evidence of faulty organ functioning. On the basis of my monkey records, I can agree with Rock's contention, based on clinical experience, that nonovulating females tend to be more irregular than fertile, ovulating individuals. With the spread of the "safe period" or "natural" method of birth control, which many patients insist on practicing, it has devolved upon the physician to offer advice based on the best information obtainable. Since it is assumed that the day of ovulation may shift with the onset of the succeeding period, in other



is the outcome of a cooperative research by Dr. Inez de Allende of Argentine, Dr. Shorr of New York, and myself. Some of the facts are these:

As ovulation approaches, leucocytes and basal epithelial cells are present in the smear in reduced numbers down to zero, and large scale-like cells take their place. Several days before ovulation there appears a cell type thus far overlooked; it is present but one day, except in the absence of ovulation, when, if it appears at all, it persists for several days. It can be produced in response to estrogen administration in castrated monkeys and menopausal women. In both monkey and woman, in ovulatory cycles, in correlation with the second peak of estrogen secretion, this cell, which I would like to call the "Shorr" cell, reappears. This holds for both species. The details will be published later.

#### THE MAMMARY GLAND CYCLE

The occurrence of cyclic changes in the human breast parenchyma is likewise both affirmed and denied. For the monkey Speert has been able to demonstrate such a cycle, but only by means of successive biopsies on the same animal in the same menstrual cycle. After studying and classifying hundreds of biopsies taken by Speert and myself for various purposes at the Carnegie Colony, it was found that the individual variation in the breast often exceeded the cyclic changes in the same animal. Unlike the uterus, the breast showed great variation under the same hormonal stimulation, reflecting conditions immediately preceding a given moment of biopsy. On the contrary, the quickly regenerating endometrium reflects the endocrine level of the moment.

These facts would explain the conflicting results obtained in most human studies and also Speert's agreement with Rosenberg, who based his conclusion on successive biopsies on the same woman.

#### THE CERVIX UTERI

No one has as yet, to my knowledge, made successive biopsies on the monkey cervix comparable to the studies of Wollner in the human being. I have a collection of cervices, however, taken from autopsies; from a cursory study of these, it appears that there is a shallow cycle perhaps even less marked than that of the mammary gland.

A priori, one must postulate a cycle demonstrable histologically because of evident cyclic changes in the viscosity of the cervical secretion. For both in the monkey (Lamar and Shettles) and in women (Lamar, Shettles and Delfs) the otherwise rather thick cervical mucus changes suddenly and for but a day or two in each cycle to a thin fluid of such low viscosity that sperms penetrate at a rate of a millimeter in three minutes. This condition was frequently found also in the premenstruum, again doubtless in response to the second rise of estrogen level characteristic of the ovulatory cycle.

#### TIME OF OVULATION IN THE MENSTRUAL CYCLE

Let us not agree from the double peak of estrin level that there are two ovulations ("three in young girls") as Samuels contended. To do so we should have to discard all the sound information that has been gained from thousands of laparotomies as well as controlled observations on ovaries and uteri of women and primate animals.

luteum, there is a second rise in estrogen output, so that one may contend that here, too, menstruation is due to estrogen deprivation.

Before the last word is said on the relation of the steroidal hormones to menstruation, it will be necessary to determine the metabolism of the hormones in the body. Menstrual phenomena are pretty nearly identical in man and monkey, yet in the metabolism (destruction, transformation) of progesterone as well as estrogens the two species differ markedly. Androgens and products of adrenal cortex coming into the picture further complicate the theoretical aspects of the problem.

#### THE SPIRAL ARTERIES

Menstruation is a vascular phenomenon. The changes in the blood vessels leading to menstrual bleeding may be seen in intraocular transplants of the endometrium according to the Schochet method perfected by Markee. This investigator has given us a clear picture of the behavior of the blood vessels, spiral arteries, capillaries, and veins preceding and accompanying the menstrual flow. For these basic studies, of course, the monkey is indispensable.

Among cyclic changes in somatic blood vessels we must mention the increased fragility of the cutaneous capillaries described by Brewer. But no such general rule can apply to the arterioles of the endometrium, because, as Markee has dramatically described the process, menstrual bleeding is a strictly local affair, involving single fields supplied each by its spiral artery. Neighboring fields may not be involved until hours or days later. Under the endocrine theory of menstruation, we should expect identical response at all points at the same time.

Markee's studies have further emphasized the fact that for menstruation to occur there must first be endometrial growth (in response to hormone stimulation), then regression (due to hormone withdrawal). The regression seems essential. Menstrual bleeding does not follow regression of the endometrium in the rabbit, however, under the same circumstances; this leads one to inquire: what peculiarity of the primate endometrium is bound up with the menstrual phenomenon?

The answer to this question, so far as morphology can give an answer, lies in the spiral arteries, the structure of which has been largely cleared up by Daron. These arteries doubtless have physiologic properties peculiar to themselves, but about that we as yet know little. We do know, however, that rabbit and guinea pig endometrium does not bleed, although the transplants regress after a drop in hormone level. The bleeding that has been described in rabbit uteri (Zondek) after large doses of estrogen is pathologic and has nothing to do with menstruation.

#### THE VAGINAL CYCLE

Monkey and man further closely parallel each other in the similarity of reaction of the vaginal mucosa to estrogens and progesterone and the sequence of changes in the menstrual cycle. That there is a clear-cut cycle in the monkey was revealed by vaginal biopsies studied by Davis. Whether there is a similar cycle in women is still under dispute, with a majority of the workers claiming to have demonstrated a cycle. On the basis of vaginal smears, however, stained by the differential method of Papanicolaou as modified by Shorr, it is now possible to draw a perfect parallel between the monkey and man. This conclusion

good as 1 in 15 (and they seem to be) of curing sterility in women by means of gonadotropes, the gynecologist is probably justified to experiment further in this direction, particularly since no permanent damage has been shown to occur from the treatment.

#### PREGNANCY

Certain parallels may be drawn between man and monkey with reference also to the pregnancy cycle. I shall speak of the mechanism of implantation, the structure of the definitive placenta and the output of chorionic gonadotropes.

*Implantation.*—There is every reason to believe that cleavage and vesicle formation in man will be found quite comparable to that in the monkey when the story is now complete. The youngest human ova (Miller, Hertig I and II) are already well implanted. The chimpanzee Yerkes A is only slightly younger. The monkey vesicle begins to attach to the uterine epithelium nine to twenty-four hours after fertilization. For the present it seems safe to adopt this schedule for man, inasmuch as no fact surrounding the young human embryos thus far discovered is at variance with this assumption.

Implantation begins by virtue of the invasive action of the trophoblast, which destroys the maternal tissues. There is every indication that the tissues are digested in situ and utilized by the embryo. The syncytium, the lacunae in the trophoblast, and other features in young monkey and human embryos and in the only chimpanzee embryo known are the same. There is a minor difference only in that the ape and human vesicles dig in deeper, become "interstitial," growing villi on all sides, whereas the monkey ovum remains superficial. The definitive placenta is identical in all three species.

The invasive action of the trophoblast continues for nearly a month when the villi become vascularized and an orderly exchange between mother and fetus is possible. The "parasitic" stage is common to all three species and ends with the establishment of the fetal circulation.

#### PLACENTAL HORMONE

Common to all three species, also, is the production and excretion in the urine of a chorionic, gonadotropic hormone. First discovered by Aschheim and Zondek in man, it has since been found in the chimpanzee as well as the monkey and seems to be the same substance in all three species. In the monkey, however, it is recoverable in the blood or urine only for about a week, first appearing, as in women, about the time of the first skipped menses or about eighteen days after conception. In the chimpanzee no hormone is found in the second half of gestation. It is truly astounding that so small an object can have so large an effect that 5 c.c. of the mother's urine has a sufficient amount of hormone to give a positive reaction in a twenty-one-day-old rat.

It should be added that in no other animal than the primates has chorionic hormone been found in the pregnancy urine.

#### THE PLACENTAL SIGN

At about the time when the gonadotrope appears in the urine of the pregnant monkey, uterine bleeding occurs which simulates menstruation but is usually much lighter. This is the so-called placental sign.

I shall not discuss at length the problem of the time of ovulation in the menstrual cycle, having little to add to former discussions. The work in the monkey, including the hundreds of ovulations recorded at the Carnegie Colony, has certainly influenced gynecologic theory on this subject and stimulated observation and experiment. In the monkey, ovulation occurs almost never before the eighth day or after the sixteenth day, twelve or thirteen days being average. The time may be a little later in women, especially in longer cycles, as it is later in the chimpanzee, which has a thirty-five-day cycle and ovulates around the seventeenth or eighteenth day.

It is more than an academic question to ask if and how often does ovulation and hence possible conception occur at a time closer to the menses than the schedule experienced by the monkey or that suggested by the Ogino-Knaus theory for women. If we can experimentally change the ovulation day, perhaps we should remember that nature has already, at some time or other, performed such an experiment. We can indeed hasten ovulation with gonadotropes; twice in monkeys of the Carnegie Colony Dr. Ball caused a delay in ovulation, once with estrogen and once with testosterone injected in the middle of the cycle.

A parallel case is offered by the phenomenon of superfetation and I must confess that I used to argue that there were no authentic cases of such an event and that ovulation could not occur during pregnancy. Since Snyder and Wislocki have shown how superfetation can be produced at will, we may as well believe that by some anomalous endocrine balance superfetation occasionally occurs in nature. The mare frequently ovulates during each pregnancy although superfetation is unknown in that species, though some day a case will doubtless be found. And so the question of superfetation, as well as that on conception near or even in the menstrual period, in my judgment is an academic one and of theoretic value only, though I admit it looms large in the minds of couples practicing the safe period.

In general, however, it is certainly true that, in giving advice to his patients, the gynecologist will stick pretty close to the schedule of the monkey's alternating fertile and sterile periods of the cycle.

#### NONOVULATORY MENSTRUAL CYCLES

Gynecologists have likewise generally accepted the existence in women as in the monkey of the nonovulatory type of menstruation, conveniently termed "pseudomenstruation" (Schroeder). The existence of this type was long ago shown to occur in nature by Heape and by van Herwerden and in laboratory rhesus monkey by Corner (1923). An overwhelming number of cases, thousands of cycles, have accumulated in my protocols at the Carnegie Colony. In the summer the nonovulatory cycle is the rule.

The recognition of the condition in women seems a step in advance, for it is something to realize that a woman may be perfectly normal and yet skip an ovulation now and then. It is of further help in classifying sterility cases which seem otherwise healthy and normal.

What to do for such women is, of course, difficult to say. Rhesus monkeys have served as subjects for experiments in this field but with only partial success. Less than a dozen cases were helped in 150 attempts to cause ovulation with gonadotropes. If the chances are as

*Prolan.*—The pregnant monkey excretes anterior pituitary-like gonadotrope or “prolan” only from the eighteenth to the twenty-fifth day, the chimpanzee until about the one hundredth day, women throughout pregnancy, on a low level, except for a tremendous peak around the sixtieth day. The characteristics of the hormone seem, however, to be identical in the three species (V. S.).

*The Vaginal Mucosa in Pregnancy.*—The human vagina maintains a fairly thick, stratified mucosal lining throughout pregnancy, whereas in the monkey this assumes infantile thickness (Davis and Hartman). Since estrogen secretion seems to be maintained throughout pregnancy in the monkey (von Wagenen and Dorfman) as in women, the differences just mentioned are difficult to explain. Since progesterone antagonizes the action of estrogen on the vagina, and as the monkey “uses up” its progesterone, it is possible that the monkey vagina receives more progesterone stimulation than does the human vagina in the latter half of pregnancy. The cervix uteri, however, shows an estrogen rather than a progesterone reaction, closely simulating the human condition at parturition.

*The Decidual Reaction.*—In the monkey it is the uterine epithelium, as in the bitch it is mainly the glandular epithelium, which gives the “decidual” reaction by enlargement and multiplication of the constituent cells. The “placental plaques” are, in spite of active mitosis for a period, ultimately consumed by the ovum without leaving a trace. In man the “decidual cells” are enlarged connective tissue cells of the stroma, as in the rodents where the reaction results in large placentomas. The end result in man and monkey is, however, the same, a “primate” placenta with one-layered villi dipping into intervillous spaces filled with slowly advancing maternal blood.

The differences between monkey and man, so far as reproductive physiology is concerned, would seem of minor, the points of similarity of major, importance, which should give the monkey a high score as an experimental animal for the gynecologist.

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It was absent once in each 100 pregnancies in the Carnegie Colony. It occurs in women also, and is responsible at times for miscalculation of the date of delivery by one month. I am told by Dr. Alan Guttmacher that, in the history of 200 private patients who did not abort, bleeding or staining occurred in early pregnancy in 42 cases, in only 15, however, as early as the twenty-fifth to the fortieth day after the last menstrual period. In the monkey, blood comes from uterine glands receiving blood from vessels that have been tapped by the erosive action of the trophoblast. Because of the interstitial implantation in man, one would expect that the human uterus would lose less blood into the uterine cavity than is the case in the monkey with its superficial type of implantation.

*Ovariectomy During Pregnancy.*—Concerning this problem, the clinical experience points to the conclusion that certainly after the second month of pregnancy the corpus luteum is no longer needed for the maintenance of pregnancy. Corroborative evidence is found in my experiments with the monkey. In one report I showed that it was safe to remove both ovaries from the thirty-first day on. How much earlier, was the question which remained. Theoretically, the answer was about the twenty-fifth day, for Corner, Bartelmez, and Hartman showed that about this time the corpus luteum begins to involute to a point at which it remains almost stationary the rest of gestation. In one experiment (Monkey 637) which I reported, gestation went on in spite of castration on the twenty-fifth day, although an irregular bleeding and a blanching of the sex skin indicated a lack of hormone; but the animal recovered from this "threatened abortion" and gave birth to a normal baby at the exact day expected on the basis of the average period of gestation for the rhesus monkey, one hundred and sixty-five days. The ovaries, serially sectioned, are in my possession.

But this story has a sequel. The female nursed her baby normally, maintaining a brilliant sex skin (estrogen effect?) and bled after four months' lactation. What hormones conditioned this bleeding? Ovarian, from remnants of ovary or accessory ovary? Adrenal cortex? We shall see. Again we have the advantage over the clinician: We can, after a period of observation perform a complete autopsy at our convenience and check any theories we may have developed concerning this anomalous case: uterine bleeding in absence of ovaries.

*Rate of Development.*—For the first month the rate of development of the monkey and the human fetus is practically identical, we believe. I have utilized this generalization to line up the hundred-odd known human embryos of the first month and estimated their conception age (*Time of Ovulation in Women, Appendix*). After the thirtieth day, the monkey grows faster than the human fetus; the lines cross about the one hundredth day (Schultz).

#### SOME DIFFERENCES

*Hormone Metabolism.*—It is a striking fact that, notwithstanding the similarity of response to the steroidal hormones in monkey and man, what the organism does to the hormones differs greatly. Progesterone is not transformed into pregnanediol and, like estrone and estradiol, seems to be largely oxidized or at least does not reach the urine in amounts exceeding 5 per cent of the amount administered. An intermediate condition seems to obtain in the chimpanzee.

soon learned that his arduous application to his problem had developed unusual skill in this delicate task.

Numerous perfect embryos and their gestational sacs of known age provided the embryologists with a complete story of primate implantation and the very early development of the embryo. This monumental work provided the impetus for the fruitful contributions of clinicians in this field during the past few years. The magnificent embryos of Hertig and of our own Brewer have aided in these classic contributions. Today, the fascinating story of early implantation and early growth of the embryo has been securely established.

Obviously, although the embryology of the primate was the incentive for the work at Carnegie, the entire reproductive function provided many problems. Careful data concerning ovulation, menstruation, and their correlation were collected over many years under the most ideal conditions. The endocrinal control of the cyclical changes incidental to the reproductive function was investigated. The solution of these many problems was directly reflected in a better understanding of the normal physiology of human reproduction and the many pathologic deviations which produce the gynecologic disease with which we are confronted. The cure of some inflammatory conditions of the lower reproductive tract was the logical sequel of the demonstration of the estrogenic control of the vaginal mucosa. Dr. Hartman and his many co-workers have thus pioneered many of the achievements in gynecology.

## PREPARED PARENTS—THE CORE OF CREATIVE FAMILY LIVING

HAZEL CORBIN, R.N., NEW YORK, N. Y.

**I**N THESE days of conflict, the differences between man and man, between ideas, ideals, and ideologies are so frequently stressed that we fail to see the common ground upon which we all stand.

So in our field of endeavor for human betterment, we tend to emphasize the differences rather than the common goals toward which we are all striving.

What is our common goal?

Ask the doctor, the nurse, the public health worker, pin them down to basic facts. Ask the social worker, pin her down to the basic things, not the day-by-day aims. Ask the minister, pin him down to basic realities, not the preaching of creeds or rituals, not traditions or visions. Ask the teacher, pin him down to the basic things, not the teaching of facts, or theories, or syllogisms. Ask the soldier, pin him down to ultimate realities, not the winning of this battle nor the annihilation of that enemy. He will tell you, as will all the others, that the end of his work is a strong nation, a strong social system so that strong family life, the basic unit of our free, civilized society, may flourish. That is our common goal.

In the mists of struggle and strife and competition, we frequently miss that goal; we strive for some fetish which we, in our enthusiasm and nearsightedness, have set up. We waste energy and effort, brains

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## DISCUSSION

DR. GEORGE W. BARTELMEZ (by invitation).—Dr. Hartman's monograph on the rhesus monkey, which deals with the nonpregnant and pregnant cycle, represents the most detailed and authoritative information we have for any primate.

I would like to call attention to just one feature which has impressed me in his presentation, that is the experiments in which the time of ovulation was set back by the injection of hormones. In nonpregnant monkeys we have seen animals in which a series of normal cycles followed one another and then for reasons unknown, nothing happened for a longer or shorter period. In several of these animals the characteristic reddening of the perineal skin which is frequently associated with the growth of the Graafian follicle failed to appear as expected. I quote one case from Dr. Rossman's records: Twenty-eight days after the onset of a period the sex skin began to brighten up, reaching a maximum after seven days. Three days later the color began to fade. Nine days after this menstruation began, that is, forty-seven days after the previous onset. At autopsy on the first day the uterus and the corpus luteum showed a typical first day picture. Schroeder and others have recognized the occurrence of a similar phenomenon in women, and Markee in his observations on the growth of transplants in the eye of the rhesus monkey has also seen long postmenstrual phases of inactivity. His transplants failed in these instances to grow for various periods of time postmenstrually and then growth was resumed. The occurrence of such phenomena means that in any given case it is impossible to say precisely when ovulation will occur. Dr. Hartman's data prove statistically that ovulation is most likely to take place at the middle of the cycle, but postmenstrual periods of inactivity may intervene, and as a result, ovulation may occur any number of days after the onset of a period.

DR. M. EDWARD DAVIS.—Dr. Hartman's work has helped to pave the way for a better understanding of human physiology of reproduction and its many pathologic variations.

Embryology was in a dormant state prior to the founding of the primate colony by Dr. Streeter, Dr. Hartman and their associates at the Carnegie Institution of Embryology. The human material available for study was far too incomplete and often in such a poor state of preservation that there were large gaps in our knowledge, particularly during the early days of gestation. Even the age of many of the well-known embryos was in question. To remedy these defects it was necessary to have normal primate material representative of definite periods. To provide such a source of accurately timed specimens it was necessary to create a normal and healthy environment in which these laboratory animals could live healthy lives and breed normally, to study the entire reproductive career of the rhesus monkey, to develop experimental methods and to follow cyclical changes in the ovary and the uterus. When I first saw Dr. Hartman palpate the ovary of a monkey and describe a mature follicle, I knew that he was a visionary, but I



Can you blame the minds of John Q. Taxpayer or Constance Contributor for being addled and confused? But in addition there was confusion added to confusion. Most of the social reform campaigns began on a negative note. Poverty, sickness, graft, all these have much more of the dramatic in their appeal than health, honesty, economic sufficiency. They were played up for all they were worth.

It was done in the obstetric field. It was lamented that American mothers paid for maternity with the highest price in life in all the civilized world. Tears were shed over the 16,000 white carnations that would be worn on Mother's Day each year for mothers who died in childbirth. No one questions that public interest and public action resulted, but who does not question the unnecessary fears that were stirred in the hearts of mothers and fathers? It was done to compete with all those equally dramatic campaigns launched on the bewildered public by this agency and that association.

The Planned Parenthood movement, faced with the same conditions, shouted loud and long to be heard in the melic. The emphasis, too, was on the dramatic, the negative. "Birth Control" was the slogan. It was a tremendous job of propagandizing—such a job that, in these days of constructive appeals, people may still be thinking only in terms of the negative, of keeping babies from being born.

All who have been converted to the glorious light of the positive appeal from the darkness of the negative, have a big task ahead to supplant the negative with the positive message; to tell the story that Planned Parenthood can mean just as much in helping husbands and wives who are infertile to have children.

All who have indulged in negative emphases are finding, and will continue to find for a long time to come, the results of past campaigns flying back as Australian boomerangs. Right now I am thinking of those 10 per cent of all married couples who are sterile, many of whom, under the aegis of "Birth Control" teaching, have been needlessly practicing contraception for years. What do you think they're going to say when they learn from the broader and more comprehensive educational efforts that they needed no contraceptive? Their plight reminds me of the tale of Moses Meers:

There was a man who had a clock,  
His name was Moses Meers.  
And every day he wound that clock  
For eight and twenty years.  
Then, one day he found that clock  
An eight-day clock to be.  
A madder man than Moses Meers  
I never hope to see.

We have all matured enough in our thinking after these disillusioning and educating experiences of competition and free-for-all struggle, to work out ways and means of eliminating the weaknesses and dangers of yesteryear. We need today an organic getting-together in thought and philosophy as well as in action. We need to find the common ground upon which we all stand. Just as our democracy is changing and the policy of economic laissez faire is on the way out, so in social progress the policy of laissez faire among those agencies working for human betterment is doomed to extinction.

and brawn. We are like a group of disunited allies, fighting the same cause, but unwilling to trust each other, to carry out a unified campaign of action.

For years, each group among us has had an ax to grind, an emphasis to put upon a special field of interest. The group with the most eye-catching phrase, which presented its case most enticingly, secured the attention and the action of the public. The result has been that some phases of the work for sound family living received overemphasis and other equally important, or perhaps even more important, phases received underemphasis.

In one community, perhaps, the need for sanatoria for tuberculous patients might have been most attractively and forcefully presented. In that particular community there might have been more crying needs to which the public paid little or no attention because those needs lacked vigorous champions.

In another community, it might have been a greatly overemphasized campaign for more funds for the control of infantile paralysis, or a pressure group for prenatal clinics unrelated to adequate delivery service. In other communities charity organization groups or housing associations or prison reform societies pressed their claims most successfully for public interest and support.

This struggle and competition for public attention with its emphasis on the dramatic had its other and more pernicious aspects. How avidly various groups presented their cases only to find that suddenly the basis of their appeals had been swiftly and effectively thrown into the scientific ash can. Facts were facts no longer and public enthusiasm sometimes turned into public antagonism or apathy.

We heard such slogans as, "A clean tooth never decays" and "Be healthy—take a bath at least once a week"—and then suddenly we heard them no more.

The egg and milk cure for tuberculosis had its advocates, but they vanished when science proved that the disease is caused by a germ and requires more than diet to combat it. Then came the outdoor life, fresh air, outdoor sleeping tents and pavilions amid the snowy peaks of the Adirondacks or the dry wastes of Arizona. And great health resorts grew up in these localities. People just took for granted, under the tutelage of propagandists, that unless you went to those spots on the map your chances for removing the spot on the lung were very few indeed. Then again the chorus was changed. "Why go away?" became the theme. "You can get well in a local sanatorium." In response to this new emphasis, a great new system of local sanatoria for tuberculosis has grown up and the once popular health resorts have languished.

Or take the field of maternity care. "Go to the hospital. Have your baby in a hospital!" was shouted from the housetops from coast to coast. Somehow in the enthusiasm for hospitalization and the struggle for the public interest, the million and more mothers who had no access to a hospital of any kind were forgotten, and many a mother had her baby with unnecessary fears and dread in her heart, because she lived too far away from a hospital or had no money to go to a hospital. Then, suddenly we heard another chorus and it came right from the hospitals themselves. Said the American Hospital Association, "The safest place in the world to have a baby is a good hospital—but the most dangerous place is a poor hospital!"

life? What of the economic factors, the health factors, the nutrition factors, the hereditary factors in the coming of children? What of the instruction of young people in the construction and function of their own bodies? What of the proper presentation of the conception, growth and birth of a baby in the education of every adolescent? What of the understanding of young married people about abortion, its dangers, about sterility, its causes? What of the freedom of parenthood, freedom to limit families and freedom to have children?

I see small hope of finding answers to these questions, of providing the right kind of education for parenthood, of helping America's parents to make the wisest and best decisions about their family life, when the brand of trust and faith and confidence which we hope to inculcate in tomorrow's young people does not yet exist among the agencies which do the work.

Now I am an optimist. I see the end of overemphasis, of needless and fruitless competition. I see the time coming when all the facts in their right relationships may be presented to the public for clearheaded action. What I am talking about may not be for today, but surely for tomorrow. We have much to learn, all of us. We have to learn to think together, to work together, to do more basic research together in the teaching of the public. We have got to learn to see the relation of our job to the whole picture. Some of the things we do will have to increase; some will have to diminish, some must vanish. We shall have to be able to see our specialized causes put in their relative positions. If we are really sincere about working together, if we are willing to make sacrifices, if our interest is in serving the people and not promoting a particular organization—IF . . . I say, then our efforts to make for sounder, happier, healthier family living in America will be crowned with achievement.

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EDITOR'S NOTE: This paper was read at the recent annual meeting of the Birth Control Federation of America in a symposium on Planned Parenthood. Miss Corbin is the nationally known director of the Maternity Center Association of New York and presents a controversial subject, which now occupies so much public interest, in such a forceful and illuminating fashion, that it deserves the attention of the medical reader. We, therefore, are pleased to publish it in the columns of the JOURNAL.

Now, I am not saying that all our experiences and competitions were not a necessary part of normal growth. I think many of them were. Perhaps we needed an Antediluvian Period, a Caveman Age where the survival of the fittest strengthened and toughened thoughts and tools. Albert Deutsch of the newspaper, P.M., recently lamented the passing of the giants of social reform and the great popular movements which they led, the Jacob Rises, the Mary Richmonds, the Jane Addamses, the Trudeaus. They were undoubtedly important to social progress. They were important to their day. But really, I do not lament the fact that we have no giants in this year of our Lord 1942. We are beyond the stage of great campaigns for one thing and another. We are coming to the day in our social progress when we must integrate our efforts and our thinking.

The first result of these popular movements of the past was to divide up living and even dying, into segments. We had clinics for this and hospitals for that, associations for one thing, societies for another. Many a maternity patient who received prenatal care in its most literal sense, that is, care that was focused only on her reproductive functions, died from tuberculosis or diabetes or cancer soon after the coming of her baby. Each segment of life was isolated from the other segment and the results on family living were not even considered by the rank and file of organizations and workers.

In the field of obstetrics, for instance, for centuries attention was given to labor and delivery. Only in relatively recent times was the relation of abnormalities and complications of pregnancy associated with difficulties at birth. Then a campaign for prenatal care was launched. But the train of thought could not stop there. The concept of obstetrics was extended to include post-partum care. Doctors and health workers began to realize that the health of the parents before pregnancy, yes, even before marriage, played an important role in safety in childbirth. The health of mothers and fathers depended upon habits and attitudes which led right back to family living. The coming of a baby is not a segment of life, but life itself. It cannot be studied apart from the sum total of living. Thus the movement broadens and generalizes as the years pass.

This is true of every other specialized campaign. I need not trace the development of the charity organization movement into the family welfare movement; or the birth control movement into the planned parenthood movement; or the blossoming of religious thought from the confines of narrow creeds to the expansiveness of the "abundant life," or the growth of the concept of teaching from the three R's to preparation for living.

We are all on common ground, having arrived there through devious paths and strange interludes. The groundwork has been laid for the development of sound, constructive, joint efforts for the preparing of parents to make family life the creative influence it should be in our society.

The whole basis of constructive family living depends upon the knowledge, the spirit, the character of parents and their ability to work out their family salvation with love and understanding.

Today all engaged in human betterment have many questions to think through and answer together. What of the spiritual values of family

# Department of Reviews and Abstracts

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CONDUCTED BY HUGO EHRENFEST, M.D.

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## Selected Abstracts

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### Endometriosis

1. Philipp, E., and Huber, H.: The Origin of Endometriosis, Including a Contribution to the Pathology of the Interstitial Portion of the Tube, *Zentralbl. f. Gynäk.* 63: 7, 1939.
2. Philipp, E., and Huber, H.: The Clinical Features of Endometriosis in the Light of the Results of Recent Investigation, *Zentralbl. f. Gynäk.* 63: 482, 1939.
3. Huber, H.: Myomata (as related to) Sterility and Fertility With a Further Contribution to the Significance of Tubal Endometriosis, *Zentralbl. f. Gynäk.* 63: 760, 1939.
4. Philipp, E., and Huber, H.: The Extension of Corpus Carcinoma (to the Tube), *Zentralbl. f. Gynäk.* 63: 2153, 1939.
5. Philipp, E., and Huber, H.: Summary, *Zentralbl. f. Gynäk.* 63: 2448, 1939.

This series of studies appears to be of sufficient importance to justify a report at length. Since they make a continuous series and since there is much repetition in each, it is perhaps best to abstract them together.

The first report begins with a brief summary of the various theories of the origin of endometriosis. The major difficulties in the acceptance of these theories as completely satisfactory are detailed and, in particular, attention is called to the failure to transplant menstrual endometrium and to the three well-known cases of endometriosis of the leg and arm. The authors' experiences lead them to the conclusion that the mechanism of transplantation is the most acceptable explanation of etiology. The usual site of implant is evidence in support of this view. They quote what appears to have been the case which directed their attention to the findings which are to be reported. Blood and a portion of endometrium were found free in a Fallopian tube whose interstitial portion was occluded by endometrium.

Endometrium in the Fallopian tube has been described but the actual frequency of its occurrence has not been recognized. The origin of this has been variously ascribed to transplantation (Sampson), redifferentiation (Meyer) and transplantation from a chocolate cyst (Novak). The condition is not to be confused with adenomyosis tubae or salpingitis isthmica nodosa.

In this condition of endometriosis of the tube, it is usual that only the interstitial portion of the tube is involved. The endometrium is continuous with that of the uterine cavity. The lumen of the tube becomes eccentric. Partial or complete closure is produced and the lumen may end in a blind sac. This endometrium undergoes cyclical changes. It may become characteristic of cystic glandular hyperplasia. Squamous epithelial change is occasionally seen. The endometrium may be in the form of a polyp.

# Society Transactions

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## CHICAGO GYNECOLOGICAL SOCIETY

*MEETING OF JANUARY 16, 1942*

The following papers were presented:

**Low Cervical Cesarean Section. A Motion Picture in Color.** Charles E. Galloway and Philip H. Smith.

**Some Contributions of Research on Primate Animals to Gynecological Theory.** Carl G. Hartman (by invitation). (For original article, see page 156.)

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## WASHINGTON GYNECOLOGICAL SOCIETY

*MEETING OF NOVEMBER 22, 1941*

**An Evaluation of the Various Types of Cesarean Section.** By Dr. Edward A. Schumann of Philadelphia (by invitation).

**Prolapse of the Uterus During Pregnancy and Labor.** By Dr. Samuel Dodek.

*MEETING OF JANUARY 24, 1942*

The following papers were presented:

**Methods for the Relief of Shock in Obstetrics.** By Dr. Norris Vaux of Philadelphia (by invitation).

**Vesicovaginal Fistula.** By Dr. John Darner.

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## PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY

*MEETING OF FEBRUARY 2, 1942*

The following case report was presented:

**Cornual Pregnancy.** By Dr. F. D. Frank.

The following papers were presented:

**Pelvic Pain.** Dr. W. A. Wolf, discussion by Dr. Morris Cohen (by invitation).

**Comparative Maternal Mortality in American Cities With a Population of 500,000 Plus.** By Dr. P. E. Marks (by invitation).

2. Endometriosis without direct continuity with the endometrium corporis—secondary endometriosis.
  - (a) Intraperitoneal spread to the ovary, uterus, peritoneum, cul-de-sac, etc.
  - (b) Extraperitoneal spread to
    - (1) region of the uterus as the vagina to the inguinal region and the umbilicus, etc.
    - (2) distant from the uterus as extremities and (?) lungs.

A list of the frequency of involvement of various sites is given. Conditions necessary for growth and the relation of these to site, function, and age of origin are discussed. They limit its clinical appearance to the ages of sexual activity. The age distribution and average age of the authors' patients show the condition to be one of advancing age in terms of sexual activity which suggests that disturbances of ovarian function and hormonal stimulation of the uterus and its mucosa may play a part in giving rise to it.

The peculiar histolytic power of the stroma of endometriosis is discussed together with the morphologic differentiation of the usual benign and the rare malignant form. An interesting case is described in which histologic control with a time interval showed the development of a sarcoma from a benign endometriosis.

The third report deals with the relationship between the occurrence of myomas and tubal endometriosis and their effect in interference with fertility. It is pointed out that the presence of myomas tends to sterility. The mechanism of this has never been satisfactorily explained.

The first part of the paper is given over to a statistical study of the myoma-fertility relationships. As a standard for normals the figures supplied from the German census and contained in the German *Year Book* reports for women married between 1907 and 1925 is used. Those years are chosen to make the material comparable in time to the experiences of his patients. The reports are based on 10,500,000 women. For comparison with these he has 480 married women with myomas.

A great many interesting figures are given. The interested reader is referred to the text for these tables.

He concludes: (1) There is no evidence of a special predisposition in the unmarried to the development of myomas. (2) The relative fertility of women who develop myomas is decreased. (3) The last pregnancy in the myomatous woman occurs four years earlier than in the average. (4) There is no real primary sterility in the woman who develops myomas. If she marries early enough, she can conceive. She shows what appears to be a primary sterility when she marries at an age when the myoma patient is developing her secondary sterility. (5) Multiple myomas are associated with a much greater decrease in fertility and increase in sterility than the solitary myoma. (6) The patient with myomas tends to become sterile at 26 to 29 years of age. (7) The myoma shows its effect on fertility and in the production of sterility almost at the time of its origin or at least early in its development. Its major effect then is not to be explained by simple mechanics alone.

The reader will wonder what this has to do with endometriosis. The second or histologic portion of this report goes on to show that in his series, half of all the myomas investigated showed an associated tubal endometriosis as has been described above. Most of these produce complete closure of the interstitial portion of the tube. Sterility always follows this and frequently follows the incomplete closure. Ten cases are detailed. Of the whole myoma group, 54.9 per cent had an associated tubal endometriosis. This was present in 33 per cent of the solitary and 69.6 per cent of the multiple myomas. Conversely, of 73 myomas without tubal endometriosis, 29 of the cases were multiple myomas, and 44 were solitary. There is no satisfactory explanation for the association of myomas and tubal endometriosis.

Cases are described to illustrate these details. One is of particular interest in relation to what is to follow. A 33-year-old patient was found at operation to have a myoma of the uterus and disseminated endometriosis of the ovaries among other places. The fimbriated ends of both tubes were open but both interstitial portions occluded by endometrium. The remainder of the tube lining was normal.

The remainder of the reports, then, are studies which relate this tubal endometriosis to endometriosis elsewhere, to sterility, to myomas and to some other things.

"The cause of abdominal endometriosis is the above described adenomyosis and endometrial polyps in the tube." "These are not exceptional findings but have a broad importance." Of 23 cases of abdominal endometriosis which were studied, 19 showed endometrial extension to the tube, and of these, 14 showed bilateral tubal involvement. In 9 cases the endometrium was present in the tube in the form of polyps, and in 3 cases the polypoid form was bilateral. In almost all cases the fimbriated ends of the tubes were open but the interstitial portions closed. The importance of this in a consideration of the mechanism of Sampson's retrograde passage of menstrual corpus endometrium is clear.

The authors assume that the passage of endometrium from the interstitial portion of the tube to the abdomen occurs as a result of small pieces being broken off, probably as a result of tubal contraction. Thus, an association with menstruation is not necessary and endometrium may be passed in a state which is known to allow of successful implantation. The authors believe that other types of transplantation may occur but that these are rare.

One other finding is presented in support of the hypothesis. In the presence of closure of the abdominal ostia, the whole tube may become lined by endometrium. Three such cases are described and it is stated that no such cases are described in the presence of open ostia.

It is further stated that the site of implantation in the pelvis has to do with the concentration of estrin. It is assumed that the nearer the ovary, the greater the estrin concentration.

Endometriosis of the umbilicus, inguinal region and metastatic forms are still explained in the conventional manner.

In summary, then, the authors state that endometriosis arises by

1. Direct extension from the uterus, as that in the abdominal wall, parametrium, retroperitoneal connective tissue, vagina, etc.

2. Much more often (a) passage from broken off bits of endometrium from the interstitial portion of the tube which then implant (4/5 of authors' cases); and (b) less often than 2a, by passage and implantation of viable endometrium broken off by intrauterine procedures.

3. Occasional hematogenous passage.

In the second report, consideration is first given to terminology and classification. Endometriosis is defined as a condition which is characterized by the presence of uterine mucosa in areas where it does not belong. They suggest that the term adenomyosis be dropped. There is no significance in the term endometrioid since the tissue is real endometrium and not only something similar to it.

The following terminology and classification are recommended:

1. Endometriosis which is continuous with the endometrium corporis—primary (localized) endometriosis.

- (a) Endometriosis of the uterine musculature (endometriosis interna)

- (b) Endometriosis which has spread from 1a to the parametrium, retroperitoneal connective tissue, bladder, abdominal wall scars, etc.

- (c) Endometriosis which has spread to the tube and is continuous with the endometrium of the uterine cavity.



to attach itself when carried outside the uterus. The route of spread plays a minor role, dissemination taking place most frequently by way of tubes into the abdominal cavity. Possibility of hematogenic dissemination has been established by microscopic studies. Perfusion of the tissues with ovarian hormones produces more favorable conditions for implantation.

J. P. GREENHILL.

**Rintelen, P. W.: Incidence of Tubal Endometriosis in Women With Seemingly Healthy Genitalia, Zentralbl. f. Gynäk. 64: 1042, 1940.**

Rintelen studied microscopically sections of tubes of 513 women who were sterilized for various reasons. In none of them either from the history or at the time of operation had an endometriosis been suspected.

However, he discovered in 130 patients, aged between 13 and 20, 6 instances of endometriosis; in 213, aged between 21 and 30, 9 instances; in 154, aged between 31 and 40, 6 cases of endometriosis; but none in 16 patients, aged between 41 and 45.

Thus there were 21 instances of tubal endometriosis discovered in this series of apparently healthy women, an incidence of 4 per cent.

In those sections in which curettage material was mounted together with the tubal tissue, the ectopic endometrium was found to be in the same phase of cyclic activity as the true endometrium.

R. J. WEISSMAN.

**Turunen, Aarno: Clinic on Endometriosis Externa, Acta obst. et gynec. Scandinav. 19: 477, 1939.**

A group of 200 cases of endometriosis externa treated at the University Women's Clinic in Helsinki is reported. Five of these patients were treated by irradiation and 195 by laparotomy. Large endometriotic hematomas in the ovaries were met with in about 43 per cent of the cases.

Dysmenorrhea, considered to be the severest symptom, was present in 72 per cent of the cases. Rectal symptoms were observed in 46 per cent, and symptoms from the urinary bladder in 7.2 per cent of the cases. The periodicity of these symptoms was not always conspicuous. Menorrhagia and metrorrhagia were produced only by far-advanced endometriosis externa. Of the married women 90 per cent were sterile, primary sterility being present in 43.6 per cent and secondary sterility in 46.4 per cent of the cases. The correct diagnosis was made before the operation in 50 per cent of the cases.

Radical operations were performed in 43 and conservative operations in 152 cases. It was possible to preserve the capability of conception in 124 patients (63.5 per cent). The mortality rate for the operations was 0.52 per cent. Of the previously sterile women 26 (31.7 per cent) became pregnant after the operation.

J. P. GREENHILL.

**Meigs, Joe Vincent: Endometriosis—Its Significance, Ann. Surg. 114: 866, 1941.**

The author feels that Iwanoff and Meyer's theory of metaplasia of the coelomic epithelium with the production of endometrium is the correct theory. Clinic patients show less endometriosis than patients in private practice, because the former are of a social status that marries early and has children frequently. Twenty-eight per cent of the author's private abdominal operations (gynecologic) showed endometriosis as against 5.8 per cent in the Massachusetts General Hospital group. The

This finding is of significance in the therapy of sterility in the presence of myomas. The author reports 42 conservatively operated myomas in married women in active sex life. Of these only 8 subsequently became pregnant.

The tubal closure can be demonstrated by hysterosalpingography. Excluding premenstrual closure and closure by submucous myomas, all closure of the interstitial portion of the tube is due to endometriosis. This is confirmed when, in the absence of filling of the tube, the uterine shadow ends in a peak or button shape. The details of the evaluation of the x-ray findings will be reported later.

The clinical significance is obvious.

The fourth report deals with the effect of tubal endometriosis in allowing extension of corpus carcinoma. Sixty-two cases of corpus carcinoma were studied. Endometriosis of the interstitial portion of the tube at least was found bilaterally in 16 and unilaterally in 13 cases. Of these 62 cases, the carcinoma had extended to the interstitial portion of the tube in 16. In 8 of these, the remains of a primary endometriosis were found, while in the other 8, carcinoma alone was present. Eight cases are detailed.

The significance of this in attempts at treatment of corpus carcinoma by means of intrauterine radium alone is clear. It may also explain some recurrences where the surgical attack has not included removal of the tubes.

The fifth report is a short summary.

This work is an interesting and perhaps important contribution. While the originals contain much repetition and too much speculation, they should certainly be carefully read. The work would seem to justify confirmatory studies.

J. L. McKELVEY.

**Philipp and Huber: New Aspects of Pathogenesis of Endometriosis, Deutsche med. Wchnschr. 66: 1242, 1940.**

According to Philipp and Huber endometriosis develops either by continuous proliferation of the uterine mucosa or more frequently by implantation. In the majority of cases of abdominal endometriosis the origin of the implantation is the endometriosis of the interstitial portion of the tube; in the others the source is the uterine mucosa itself. The implantations of abdominal endometriosis make their way through the tube or they may utilize other available routes. Hematogenic spreading is theoretically possible. The authors on the basis of their investigations arrive at a unitary interpretation of endometriosis. They reject the theory of serosa epithelium in its original and modified form, as well as the assumption that every mesenchyma is capable of forming foci of endometriosis. They believe that local formation of foci of endometriosis as the result of tissue differentiation is no longer tenable. Their own conception is similar to that of Sampson, who was first to recognize implantation of detached fragments of uterine mucosa as the cause of endometriosis. Sampson's theory met opposition, because it erroneously presupposed that cast-off menstrual mucosa was the source. It is the living freshly built-up mucosa which is disseminated. The prerequisites in the majority of cases are the existence of endometriosis in the interstitial portion of the tube and a functioning ovary. Endometriosis does not develop before or after the period of ovarian function, except, perhaps, when ovarian hormones are administered. The importance of hormones in the development of implantation is demonstrated by the fact that they are frequently localized near the ovaries. A favorite location is the ovary itself, where so-called chocolate cysts develop. The authors were able to observe such cysts in various stages of development. They emphasize that endometriosis owes its development to the special properties of the uterine mucosa; the capacity of the cytogenic stroma to grow into deeper layers and the ability of uterine mucosa

**Portes and Varangot:** Endometriosis and Pregnancy, *Gynéc. et obst.* 40: 298, 1940.

Endometriosis in the presence of pregnancy is rare, particularly because of the high incidence of sterility in women with endometriosis, and because this condition is found chiefly in women in the fifth decade of life when conception is uncommon. Portes and Varangot report a case of endometriosis occurring during pregnancy. A biopsy performed late in pregnancy led to the wrong diagnosis of spinal cell carcinoma and a cesarean section was performed. After operation, the tissue was found to be endometriosis and not cancer. The error was due to the change which took place in the cells of the tumor because of the gestation.

A review of the literature revealed that endometriosis during pregnancy may lead to errors in diagnosis and may be the cause of serious complications. During pregnancy there are two sites of predilection for endometriosis: the uterus, and the rectovaginal septum. Often uterine endometriosis is mistaken for a fibroid. Uterine endometriosis may lead to rupture of the uterus and severe hemorrhage during delivery. Rectovaginal endometriosis may produce dystocia and necessitate a cesarean section.

De Jong and de Snoo maintain that most so-called ectopic decidual nodules which are frequently observed on the peritoneum, in the ovary and in lymphatic glands are foci of endometriosis which have undergone degenerative changes during pregnancy.

J. P. GREENHILL.

**Levi, Alexander A.:** Pedunculated Endometrial Cyst of the Uterus, *New England J. Med.* 224: 156, 1941.

The case is reported of a 39-year-old woman in whom the following gynecologic anomalies were present at the same time: a pedunculated endometrial cyst within the uterine cavity, an intramural fibroid, and a dermoid cyst of the left ovary.

After several severe uterine hemorrhages, the cervix was dilated and a bluish globular mass, about 3.5 cm. in diameter, removed. Histologic study proved it to be an unusually large endometriosis cyst, its wall consisting of endometrium and some atrophic myometrium. Pedunculated endometrial cysts are extremely rare.

HUGO EHRENFEST.

**Bazy, Blondin and Chene:** Clinical and Practical Significance of Rectal Endometrioma, *Presse méd.* 47: 785, 1939.

The authors report 2 cases of rectal endometrioma, each proved by biopsy. They draw attention to the symptomatology of these cases, a painfully acute to subacute abdomen in the premenstrual period, usually afebrile and associated with diarrhea in which mucus and blood are prominent. There may be isolated cases with premenstrual rectal hemorrhage. Other patients complain of a premenstrual pain which bears no relationship to defecation.

By means of proctoscopic examination in the premenstrual period, these small tumors are usually easily recognized but are difficult to see postmenstrually. The writers suggest a functional test by the use of folliculin hormone prior to rectal examinations in patients complaining only of a rectal neuralgia.

One patient, aged 44 years, had been treated for hemorrhoids four years before. A proctoscopic examination revealed a tumor 7 cm. on the anterior surface of the ampulla. Her natural menopause resulted in complete relief.

The second woman, aged 45 years, had a painful abdomen premenstrually for each of the preceding eighteen months. This was accompanied by an afebrile course and a bloody diarrhea. A rectal examination revealed a budlike tumor 12 cm. on the anterior ampullar wall. X-ray castration gave complete relief.

CLAIR E. FOLSOME.

significance of endometriosis is that it is a stigma of infertility, and it is due to uninterrupted menstrual cycles, because of late marriage and infrequent child-bearing.

**Wespi, J. H., and Kletzhandler, M.: Scar Endometriosis, Monatschr. f. Geburtsh. u. Gynäk. 111: 169, 1940.**

During the years 1923 to 1939, the authors observed a total of 73 cases of endometriosis in laparotomy scars. This is astonishing when we consider that only 390 similar cases have been reported in the world literature. In five of the 73 cases, a cesarean section had been performed, but in the 68 other cases, pregnancy had been interrupted by an abdominal operation. In 76 per cent of the cases, the endometriosis was located at one corner of the abdominal wound whereas in only 20 per cent it was situated in the middle. (In 4 cases, there was no note as to the location.)

The cause of the endometriosis in the authors' cases was implantation of decidua from the uterine cavity to the abdominal wound. This explanation holds true both for the early abdominal hysterotomy cases and the cesarean sections. The reason that only 5 cesarean sections were encountered as opposed to so many abdominal hysterotomy cases is that the decidua at term possesses very little tendency to grow. Furthermore a curette was not used in the cesarean sections but was employed in the other cases.

By changing the technique of their operations in such a way that no endometrium could come in contact with the abdominal wound, the authors have been able to reduce the frequency of scar endometriosis from 3.4 per cent to 0.9 per cent.

Among the 390 cases of scar endometriosis reported in the literature, the chief types of operations which preceded the endometriosis were as follows: ventrofixation, 113; cesarean sections, 41; hysterotomy, 49; other openings made in the uterus, 26; adnexal operations, 51; appendectomy, 18; and removal of vulvar vaginal and perineal scars, 43.

J. P. GREENHILL.

**Von Torzsay-Kiss: Endometriosis of Cervical Origin, Zentralbl. f. Gynäk. 64: 2257, 1940.**

It was long ago shown by Robert Meyer that heterotopic growths may arise which have their origin in the glands of the cervix. J. von Torzsay-Kiss reports a few such cases. Endometriosis arising in the cervix differs from endometriosis which has its origin in the corpus endometrium, both histologically and functionally. In corporal endometriosis the glands are lined by single-celled cylindric cells with their nuclei in the center of the cells. In cervical endometriosis, the glands are likewise lined by single-celled cylindric cells, but the nuclei are typically in the basal portion of the cells. Functionally, endometriosis of corporal origin is under the influence of the ovarian hormones, and it therefore exhibits the physiologic changes. On the other hand, in endometriosis arising in the cervix the cells have only a secretory function and secrete a mucous discharge identical with that observed in the cervix. Hence, not all endometriotic growths respond to ovarian activity. The author therefore suggests that endometriosis be classified as corporal or cervical, depending on the origin. He believes cervical endometriosis does not result from transformation of cells in situ but is due to implantation of pieces of cervical mucosa. There is ample occasion for such implantations when one considers the frequency of trauma to the cervix.

J. P. GREENHILL.

Hüssy, P.: Malignant Myoma, Zentralbl. f. Gynäk. 64: 1540, 1940.

The author reports a case in which a histologically benign tumor metastasized in a manner typical of frankly malignant growths. An obese 42-year-old para v consulted a physician for fever and precordial pain. An enlarged heart with incompetent pulmonary valve was found. Radiographs revealed peculiar lung shadows. An abdominal tumor was palpable, apparently deriving from the right ovary and a diagnosis of ovarian carcinoma with pulmonary metastases was made. At operation a myoma of over 1 kilogram weight was found attached to the uterus. A supravaginal hysterectomy was done. The patient died a cardiac death a few hours later. The metastatic nodules in the lungs showed a benign structure exactly similar to that of the uterine tumor. Small nodules were found on the leaflets of the tricuspid valve and in both lower branches of the pulmonary artery. The author emphasizes that histologic benignancy does not always signify an absence of clinical malignancy.

R. J. WEISSMAN.

Cirio, C. R.: Myometrectomy. A New Technic for the Treatment of Uterine Fibroids, Presse méd. No. 48, p. 925, 1940.

The author describes a new operative technique for the removal of fibroids from the uterus. The operation, developed in his Buenos Aires clinic, is termed myometrectomy. The tubes and the round ligaments are severed at the cornual regions of the fundus uteri. Approximately one-half of the superior mass of the fundus uteri and its accompanying tumor, if present, is excised by transverse incisions. This portion of the operation resembles the defundation technique.

The writer then proceeds to enucleate, between the uterine serosa and the endometrium, the residual portion of the fibroids and any excessive myometrium in the remaining segment of the uterus. Care is taken to preserve the residual endometrium in this lower segment. The upper ends of the endometrium are then coapted with suture. The mesial ends of the Fallopian tubes and the round ligaments are buried in the new cornual regions while the remaining superior edges of the myometrium are approximated into a new fundus-like extremity. Peritonization of the serosal surfaces concludes the operation.

Cirio has performed this operation upon forty different patients. He notes that Riberro, of Rio de Janeiro, has done nine similar operations. The writer concludes that his operation is of value in that it tends to remain a conservative procedure and coincidentally permits recurrence of normal cyclic function. The article is well illustrated with six halftone plates.

CLAIR E. FOLSOME.

## Correspondence

### Bibliography of Brenner Tumor

To the Editor:

In the June, 1942, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, page 984, the cytologic details of the Walthard rest and the Brenner tumor were described. Since publication of this article a paper by Varangot (Les Tumeurs Ovariennes du Type Brenner. Etude Anatomique, Gynéc. et obst. 38: 11, 1938) has come to my attention. In this communication findings similar to those described by me are recorded. This paper appears generally to have escaped notice, and it is with pleasure that I acknowledge this original reference to the nucleus which I have described as a fundamental characteristic of the Brenner tumor.

622 WEST 168TH STREET

NEW YORK, N. Y.

JUNE 12, 1942

D. N. DANFORTH, M.D.

**Blaikley, J. B.: Endometrioma of the Colon Causing Stricture, Proc. Roy. Soc. Med. 34: 810, 1941.**

The author describes a specimen obtained by operation, representing a stricture so small that not even the tip of the little finger could be passed. The covering mucous membrane was freely movable over the fibrous tissue as hard as a cartilage. Microscopic examination showed here and there typical islets of endometrium in the fibrous tissue.

The patient was a single woman, 40 years old, who always had a dysmenorrhea with pain in the left iliac fossa, which gradually got worse. During every menstrual period she had severe, colicky pain and was constipated. Gynecologic examination showed a slightly enlarged uterus and a tender nodule on the back of it. In the middle of the pelvic loop of the colon was found a small mass with thickened walls. It was removed after completion of a subtotal hysterectomy with bilateral oophorectomy. As a rule, in cases of endometriosis, isolated masses cause only a local puckering of the intestinal wall; complete encirclement undoubtedly must be rare.

HUGO EHRENFEST.

**Tasch, H.: Fibroma Ovarii With Endometriosis and Ascites, Zentrabl. f. Gynäk. 64: 1823, 1940.**

The author presents an interesting case of an ovarian fibroma, weighing 3 kilograms, in a 60-year-old woman. On opening the abdomen approximately 10 liters of serous fluid were released. Histologic studies showed the presence of endometrial tissue with cystic glandular hyperplasia. Although ovarian fibroma and ascitic fluid are not uncommon, the author was unable to find reports of endometriosis within a fibroma.

R. J. WEISSMAN.

### Myoma

**Grosbeck, W., and Pool, R. M.: Similar Fibroid Tumors Occurring in Identical Twins, South. M. J. 33: 1090, 1940.**

A paper of McFarland and Meade published in 1932 stimulated interest in this unusual condition. In it they stated that tumors arising in one twin of an identical pair must occur similarly, simultaneously and symmetrically in the mate. The authors feel that their brief case report represents a contribution to the literature on the subject, since they were unable to find a single record of a similar condition.

The patients considered in this paper were colored, 24-year-old identical twin sisters. In all their physical characteristics and mannerisms there was a remarkable similarity. One of them had noticed enlargement of the lower abdomen for two years. Upon admission she complained of pain in that region, and stated that she had been nauseated and vomiting for several days. Menses were irregular and profuse. Her uterus was enlarged by multiple fibroid tumors, and it extended above the umbilicus. The twin sister had been aware of a prominence of the lower abdomen for only a month; there was some frequency of urination and dysuria of one week's duration. Nodular distortion of the uterus by fibroid tumors brought the tumefaction to the level of the umbilicus. Both patients had a supravaginal hysterectomy, and they made uneventful recoveries. Their anesthesia charts showed a similarity in pulse rate, systolic and diastolic pressures. The histologic diagnosis was simple multiple leiomyomas with considerable myxomatous degeneration in one of the tumors.

This report includes a comprehensive bibliography.

ARNOLD GOLDBERGER.

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### Erratum

Throughout the article by Paul C. Roberts entitled "Intravenous Administration of Basergen During the Third Stage of Labor," p. 849, of the May issue of the JOURNAL, the word Basergen should be Basergin.

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\*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL.





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TABLE OF CONTENTS ON PAGE 6

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## CONTENTS FOR AUGUST, 1942

### Original Communications

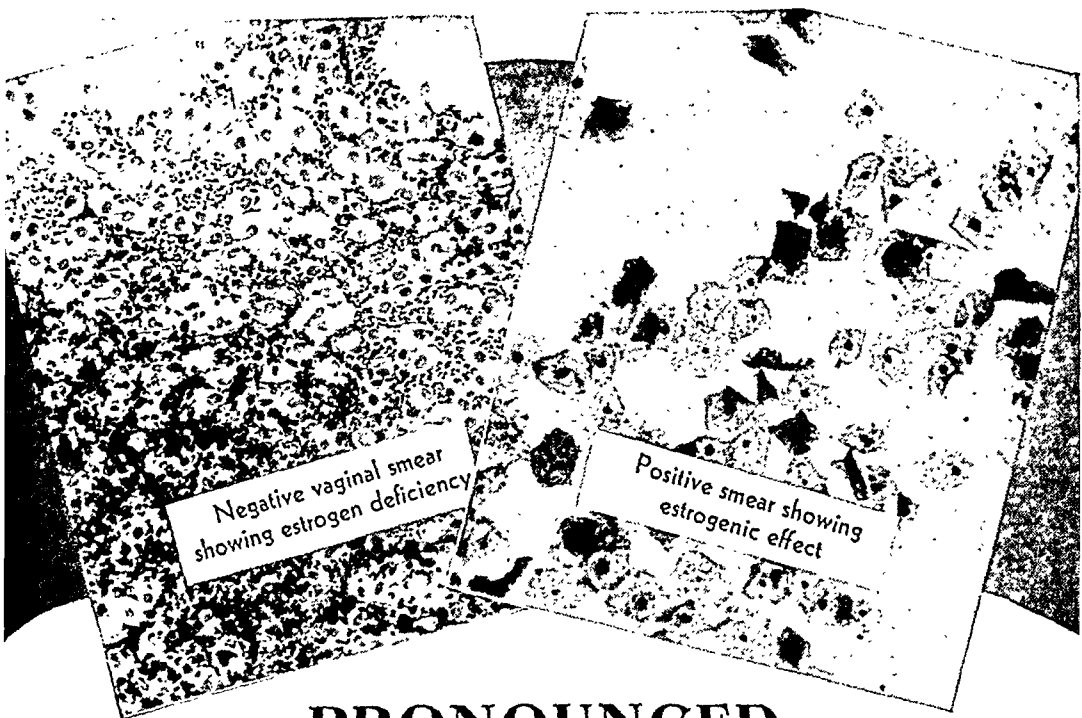
|  |     |
|--|-----|
| The Problem of Unsuspected Tuberculosis in Pregnancy. C. Wesley Eisele, M.D., William B. Tucker, M.D., Chicago, Ill., Robert W. Vines, M.D., Rochester, Minn., and John L. Batty, M.D., Hibbing, Minn. ....  | 183 |
| Progress in Myomectomy. I. C. Rubin, M.D., F.A.C.S., New York, N. Y. ....  | 196 |
| Sources of Error in the Detection of Ovulation. Leon Krohn, M.D., Joseph Harris, M.D., and Oscar Hechter, B.S., Los Angeles, Calif. ....   | 213 |
| Electrometric Timing of Human Ovulation. Louis Langman, M.D., New York, N. Y., and H. S. Burr, Ph.D., New Haven, Conn. ....  | 223 |
| Prostigmine Methylsulfate and Delayed Menstruation. L. B. Winkelstein, M.S., M.D., New York, N. Y. ....  | 231 |
| Conservative Treatment of Pelvic Inflammation With the Newman Thermo-Flo. Frederick H. Falls, M.S., M.D., Edward C. Bernell, M.S., M.D., and Disraeli Kobak, M.D., Chicago, Ill. ....  | 240 |
| Vaginal Iontophoresis of a Choline Compound. Adolph Jacoby, M.D., F.A.C.S., and Maurice G. DerBrucke, M.D., F.A.C.S., New York, N. Y. ....   | 250 |
| Experimentally Produced Fibroids in the Guinea Pig and Their Possible Analogy to Myomas in the Human Being. Rudolph Marx, M.D., F.A.C.S., Samuel Glass, M.D., and Alex Shulman, M.D., Los Angeles, Calif. ....   | 259 |
| Clinical Observations in Treatment of Nausea and Vomiting in Pregnancy With Vitamins B <sub>1</sub> and B <sub>6</sub> . Raymond S. Willis, M.D., Watt W. Winn, M.D., A. Truett Morris, M.D., A. A. Newsom, M.D., and Warren E. Massey, M.D., Dallas, Texas .... | 265 |
| Vitamin E and Premature Labor. Evan Shute, B.A., M.B., F.R.C.S.C., London, Ont. ....   | 271 |
| Mortality of Prematurely Born Infants. A. W. Diddle, M.D., and E. D. Plass, M.D., Iowa City, Iowa ....   | 279 |
| The Estrogenic Properties of Dihydrostilbestrol (Hexestrol). Roland E. Bieren, M.D., and Beverley C. Compton, M.D., Baltimore, Md. ....  | 287 |
| Vaginal Trichomoniasis. Ray E. Trussell, M.D., and Mary E. Wilson, B.A., in Cooperation With F. H. Longwell, M.D., and K. A. Laughlin, M.D., Iowa City, Iowa ....  | 292 |
| Methods for the Objective Evaluation of Estrogen Therapy in the Menopause. Henry G. Bennett, Jr., M.D., Oklahoma City, Okla. ....  | 296 |
| The Diagnosis and Treatment of Carcinoma of the Corpus Uteri Based on Experiences at the Woman's Hospital. George Gray Ward, M.D., F.A.C.S., F.R.C.O.G. (Hon.), New York, N. Y. ....   | 303 |
| Clinical Psychiatric and Psychoanalytic Study of a Case of Male Pseudohermaphroditism. Jacob E. Finesinger, M.D., Joe V. Meigs, M.D., and Hirsh W. Sulkowitch, M.D., Boston, Mass. ....  | 310 |
| Death Due to Intraperitoneal Rupture of a Strictured Lymphogranulomatous Rectum During Parturition. W. E. Pollard, M.D., and H. Hellendall, M.D., New York, N. Y. ....   | 317 |
| Endometrial Cyst of the Groin Associated With a Decidual Reaction in the Appendix. G. C. Milnor, M.D., and I. L. Tilden, M.D., Honolulu, T. H. ....  | 324 |
| Bilateral Dry Gangrene of Both Lower Extremities Due to Ergot. Abraham S. Velkoff, M.D., and A. Drew Ferguson, M.D., Atlanta, Ga. ....   | 331 |
| Bilateral Ovarian Carcinoma Associated With Intrauterine Pregnancy. Lester J. Bossert, M.D., Cincinnati, Ohio ....   | 336 |
| Unilateral Twin Ectopic Pregnancy. A. F. Lash, M.D., Ph.D., and J. D. Kaufman, M.D., Chicago, Ill. ....  | 342 |
| A Simplified Method of Glycogen Estimation in Uterine Mucosa for Clinical Purposes. Bernhard Zondek, M.D., and Benjamin Shapiro, M.D., Jerusalem, Palestine ....   | 345 |
| A Review of the Caldwell-Moley Method of Roentgen Pelvic Mensuration With a Correlation of New Technical Procedures. Robert Taylor, Hartford, Conn. ....   | 348 |
| A Simple Apparatus for Resuscitation of the Newborn. F. A. D. Alexander, M.D., and Charles E. Martin, M.D., Albany, N. Y. ....   | 351 |

### Correspondence

|                      |     |
|----------------------|-----|
| Correspondence ..... | 355 |
|----------------------|-----|

### Department of Reviews and Abstracts

|  |     |
|--|-----|
| Selected Abstracts—Mammary Glands .....                | 357 |
| Item—American Board of Obstetrics and Gynecology ..... | 363 |



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rapidly in the untreated state. Therefore it is important to recognize early active lesions."

It has become well recognized that dependence on the presence of symptoms and of abnormal physical findings is frequently quite inadequate for the detection of pulmonary tuberculosis. Many cases of tuberculosis reach an advanced stage before any symptoms are produced, and it is the exceptional case in which minimal lesions produce notable symptoms. Only rarely do symptoms occur until the disease has advanced into the stage of tissue necrosis. It is significant that more than 80 per cent of all cases of tuberculosis reported to health departments are already in an advanced stage.<sup>2</sup>

The inadequacy of even the most skilled physical examination in detecting the presence of pulmonary tuberculosis likewise has become a widely accepted fact.

Kayser-Petersen's<sup>3</sup> extensive review indicated that from 10 to 60 per cent of all cases of tuberculosis found on x-ray examination had been missed on physical examination. Bloch<sup>4</sup> estimated that more than one-third of all cases of clinically important chest disease are missed on physical examination. He now believes that this estimate is too conservative. Sampson and Brown<sup>5</sup> carefully studied 1,004 patients with tuberculosis at the Trudeau Sanitarium. They found no physical signs of disease in 39.6 per cent of the patients and physical signs indicating less disease than the roentgenogram in an additional 36 per cent.

Thus, it would seem to be evident that physical examination of the chest alone should be eliminated as a reliable tuberculosis case-finding method.

In recognition of the above considerations, fluoroscopy of the chest was introduced as a routine procedure for the patients attending the prenatal clinic of the Chicago Lying-in Hospital in 1934. All patients were invited to attend the chest clinic of the University of Chicago Clinics where the examination was made without charge. The fluoroscopies were performed by members of the staff of the chest division. Patients having definite or suspected lesions at fluoroscopy were referred for stereoscopic chest roentgenograms and for further investigation in the chest clinic. Due to difficulties in inducing patients to make a special trip to the clinics for fluoroscopy, only 64 per cent of the clinic group were fluoroscoped during the first three years of the program. When the results of these three years were compiled, the incidence of 1.06 per cent of unsuspected clinically important tuberculosis found by fluoroscopy seemed so important that efforts were made to extend the survey to all patients attending the prenatal clinic. Since it was agreed by the obstetricians and internists concerned that this program was beyond the experimental stage, plans were made to include routine chest fluoroscopy as a permanent part of the regular prenatal care. Since February, 1941, a fluoroscopy room staffed by members of

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## Original Communications

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### THE PROBLEM OF UNSUSPECTED TUBERCULOSIS IN PREGNANCY

INCIDENCE BY ROENTGENOLOGIC TECHNIQUES COMPARED WITH  
INCIDENCE OF UNSUSPECTED SYPHILIS

C. WESLEY EISELE, M.D., WILLIAM B. TUCKER, M.D., CHICAGO, ILL.,  
ROBERT W. VINES, M.D., ROCHESTER, MINN., AND  
JOHN L. BATTY, M.D., HIBBING, MINN.

*(From the Department of Medicine, University of Chicago and the Chicago  
Lying-in Hospital)*

WHEN pregnancy occurs in a woman who has tuberculosis, a serious problem confronts the physician. Although opinions differ concerning methods of treatment, there is common agreement as to the seriousness of the condition and as to the necessity for close supervision of the patient by both obstetrician and internist. In most instances, the woman with active tuberculosis should not undertake the added burden of pregnancy, both because of the risks incurred during gestation and because of the post-partum implications to both mother and child. To avoid disaster, the tuberculous woman who does become pregnant requires the best obstetric and medical care that is obtainable. As an obvious corollary to this, recognition of the disease is essential before the pregnant woman can benefit from this special medical attention; the earlier during pregnancy that the disease is discovered, the better is the outlook for the patient. As Schwarz<sup>1</sup> has said “. . . it must be borne in mind that unrecognized active tuberculosis in pregnancy will progress

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their “Original Communications.”

It will be noted that approximately 3 of 8 women were initially examined in the first trimester, when therapeutic abortion may best be done when indicated, but that only approximately 2 of 8 women found to have clinically important tuberculosis were initially examined at this stage. In not all women with clinically important tuberculosis is therapeutic abortion advisable or necessary, but the lateness of diagnosis in the period of gestation proved an obstacle to the optimum management of an appreciable number of cases. Therapeutic abortion was performed two times in this series and advised in an additional patient. Sterilization was done four times and advised in three additional patients.

# INCIDENCE PER CENT

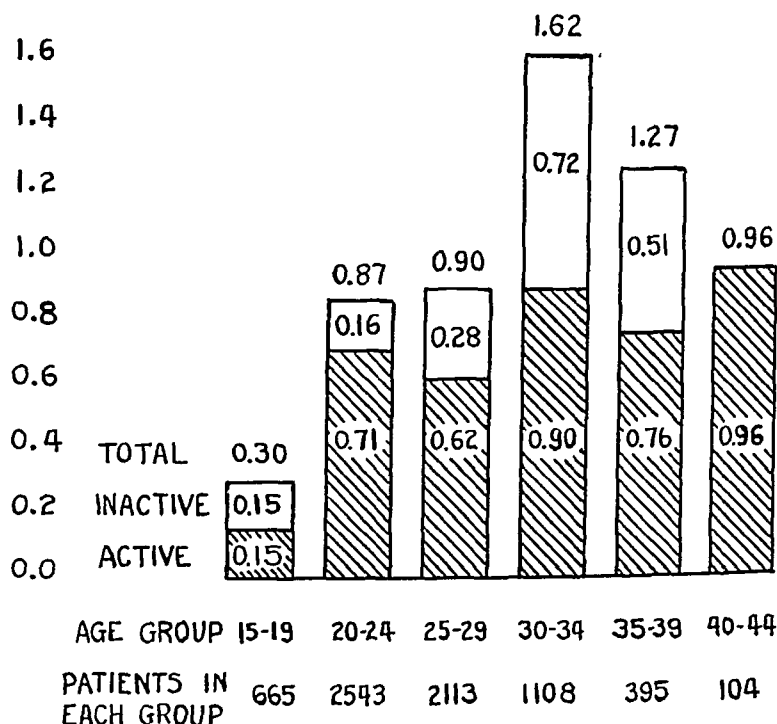


Fig. 1.—Incidence by age of unsuspected clinically important pulmonary tuberculosis, active and inactive, showing the increasing incidence with age, particularly of active tuberculosis.

The results of the prenatal fluoroscopic survey covering the period from Feb. 14, 1934, to April 1, 1937, have been reported in this JOURNAL.<sup>6</sup> The present study presents the data for the period from April 1, 1937, to July 1, 1941. The data of both periods are presented in parallel columns (I and II) and are summarized in Column III of Table I. Although routine chest fluoroscopy provides valuable working information in conditions other than tuberculosis, notably in heart disease, for purposes of this paper only tuberculous lesions will be considered.

The classification of tuberculous lesions is subject to numerous variations. For practical purposes, we have divided the lesions discovered at

the chest division and physicians trained by the chest division has been an integral part of the prenatal clinic, and all patients are fluoroscoped as a part of their initial examination. Those found to have definite or suspected lesions, in addition to those patients with known tuberculosis or with tuberculosis discovered at the initial examination by history taking and/or physical examination are referred directly for stereoscopic roentgenograms.

#### MATERIAL AND RESULTS

The patients attending the prenatal clinic are all of the white race. Although none of them are private patients, they do not represent the lowest economic strata inasmuch as most of them pay for at least part of their obstetric care and most of them are delivered in the hospital, usually paying part or all of the hospital fees.

The average age of the patients fluoroscoped during pregnancy was 25.8 years, with a standard deviation of 5.5 years. The distribution by age groups of the 6,928 women examined between 1937 and 1941 was as follows:

| AGE GROUP   | NO.   | PER CENT |
|-------------|-------|----------|
| 15-19 years | 665   | 9.6      |
| 20-24 years | 2,543 | 36.7     |
| 25-29 years | 2,113 | 30.5     |
| 30-34 years | 1,108 | 16.0     |
| 35-39 years | 395   | 5.7      |
| 40-44 years | 104   | 1.5      |
| Totals      | 6,928 | 100.0    |

Incidence of clinically important tuberculosis was found to rise with age, as has been found to be the case in other studies. This was especially true of *active* tuberculosis, less true of inactive clinically important tuberculosis, where a definite peak was found in the thirty to thirty-four age group. These findings are illustrated in Fig. 1.

Recognizing the importance of the discovery of tuberculosis as well as of other factors complicating pregnancy as early as possible during gestation, obstetricians have for years stressed the desirability of patients reporting to their physician in the early months of pregnancy. An analysis of the 6,928 women examined between 1937 and 1941 as to the stage of gestation at which they first reported to the prenatal clinic, and when, therefore, they had their initial chest fluoroscopy, shows that the average woman reported when she was 4.53 months pregnant. The distribution of the stage of gestation at the time of first examination is shown graphically in Fig. 2. Similar analysis of those patients found to have clinically important tuberculosis revealed that there was a tendency for these cases to report somewhat later in the gestation period on the average than did the entire group. The figures were as follows:

|                                   | PER CENT EXAMINED IN |                  |                 |
|-----------------------------------|----------------------|------------------|-----------------|
|                                   | FIRST TRIMESTER      | SECOND TRIMESTER | THIRD TRIMESTER |
| Total group (6,928 cases)         | 37.9                 | 42.1             | 20.0            |
| Clinically important tuberculosis | 25.4                 | 52.2             | 22.4            |



TABLE I. INCIDENCE OF UNSUSPECTED AND KNOWN TUBERCULOSIS AND SYPHILIS IN PREGNANT WOMEN AT CHICAGO LYING-IN HOSPITAL, IN THE PERIODS 1934 TO 1937 AND 1937 TO 1941

|  | I<br>PREVIOUSLY RE-<br>PORTED DATA<br>FEB. 14, 1934<br>TO<br>APR. 1, 1937 |                         |                         | II<br>PRESENT STUDY<br>APR. 1, 1937<br>TO<br>JULY 1, 1941 |                         |                         | III<br>SUMMARY OF<br>ENTIRE SERIES<br>1934-1941 |                         |                         |
|--|---|-------------------------|-------------------------|---|-------------------------|-------------------------|---|-------------------------|-------------------------|
|  | NUMBER  | PER CENT<br>FLUOR. PTS. | PER CENT<br>CLINIC PTS. | NUMBER  | PER CENT<br>FLUOR. PTS. | PER CENT<br>CLINIC PTS. | NUMBER  | PER CENT<br>FLUOR. PTS. | PER CENT<br>CLINIC PTS. |
|  |   |                         |                         |   |                         |                         |   |                         |                         |
| Patients attending the prenatal clinic   | 6,298   |                         | 100                     | 8,808   |                         | 100                     | 15,106  |                         | 100                     |
| Patients fluoroscoped  | 4,040   |                         | 64                      | 6,928   |                         | 79                      | 10,968  |                         | 73                      |
| <i>Tuberculosis:</i>   |   |                         |                         |   |                         |                         |   |                         |                         |
| <i>Unsuspected tuberculosis of clinical importance discovered by routine fluoroscopy</i> |   |                         |                         |   |                         |                         |   |                         |                         |
| Active   | 28  | 0.69                    |                         | 46  | 0.66                    |                         | 74  | 0.67                    |                         |
| Inactive   | 15  | 0.37                    |                         | 21  | 0.30                    |                         | 36  | 0.33                    |                         |
| Total  | 43  | 1.06                    |                         | 67  | 0.96                    |                         | 110   | 1.00                    |                         |
| Known tuberculosis (including tuberculosis discovered by methods other than fluoroscopy) | 49  |                         |                         | 50*   |                         |                         | 99  |                         |                         |
| Total tuberculosis   | 92  |                         | 1.46                    | 117   |                         | 1.33                    | 209   |                         | 1.38                    |
| <i>Syphilis:</i>   |   |                         |                         |   |                         |                         |   |                         |                         |
| <i>Unsuspected syphilis</i> (discovered by routine Wassermann and Kahn tests)            | 55  |                         | 0.87                    | 27†   |                         | 0.30                    | 82  |                         | 0.54                    |
| Known  | 39  |                         | 0.62                    | 64‡   |                         | 0.73                    | 103   |                         | 0.69                    |
| Total syphilis   | 94  |                         | 1.49                    | 91  |                         | 1.03                    | 185   |                         | 1.23                    |

\*Eighteen additional cases of known tuberculosis delivered in the hospital, 9 private patients and 9 patients who did not attend prenatal clinic.

†Thirteen of these patients were discovered to have syphilis during this pregnancy elsewhere before coming to prenatal clinic. There were 8 additional patients with syphilis delivered in the hospital, 4 private patients and 4 who did not attend prenatal clinic.

‡In addition there were 2 private patients and 10 hospital patients with known syphilis.

restricted according to the needs of the individual case. Naturally, the patients with active disease give the greatest concern.

The group of patients with clinically unimportant disease includes those with calcified and calciocaseous lesions which appear to be healed, and minimal fibroid lesions which appear inactive. In general, included in this category are lesions which, after investigation and observation, show satisfactory x-ray criteria of healing and are thought to manifest little likelihood of reactivation due to pregnancy. There were 62 patients in this group, and they were judged to require no special treatment. This group did not include individuals with a calcified primary complex although these are considered to be clinically unimportant. For the most part, such primary calcifications are recognized and identified at fluoroscopy and further study is not made.

fluoroscopy into *clinically important* and *clinically unimportant* tuberculosis. The clinically important tuberculosis was further divided into *active* and *inactive* lesions. The classification of each case was made on the basis of a survey of all facts known concerning the patients, clinical, laboratory, and x-ray, by a team of two or three consulting physicians.

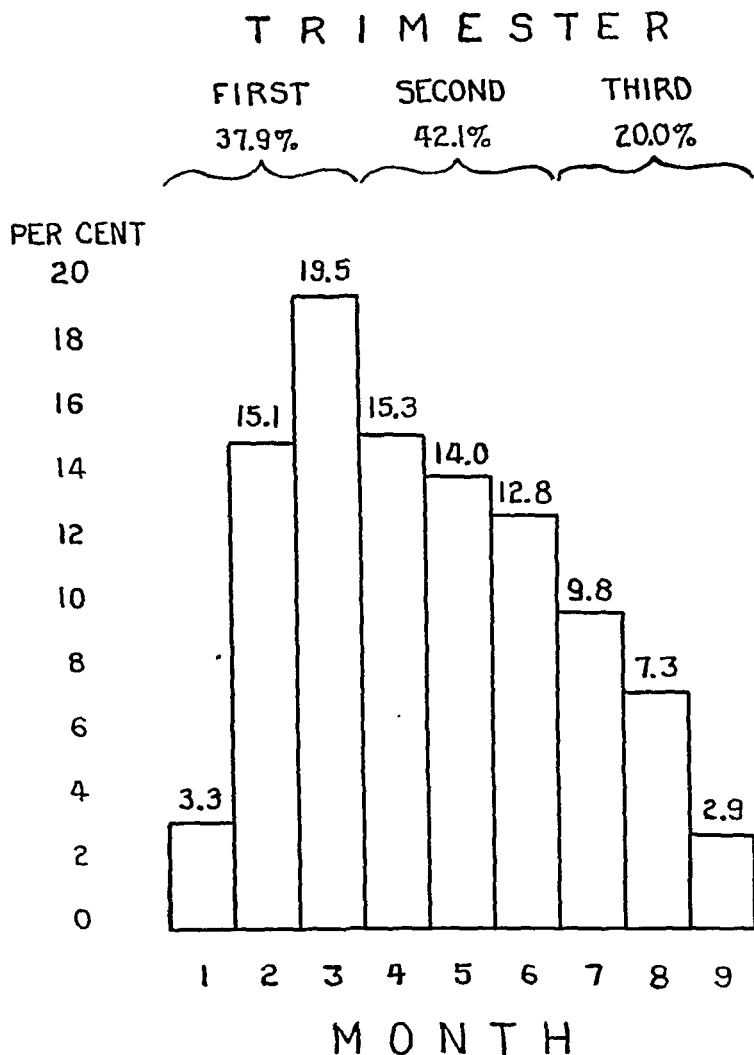


Fig. 2.—Distribution of stage of gestation when patients appeared for initial prenatal and fluoroscopic examination.

The patients classified as having clinically important tuberculosis include those with active disease, and those with the disease in an inactive stage but such that reactivation during pregnancy or the puerperium is a definite menace. Such cases will include those patients without symptoms or physical findings but who are found on x-ray examination to have tuberculous lesions which do not as yet give satisfactory evidence of healing by fibrosis and/or calcification. All of the patients in this classification are followed closely and their physical activities are

TABLE II. THE INCIDENCE OF TUBERCULOSIS IN OBSTETRIC PATIENTS IN INSTITUTIONS NOT EMPLOYING CASE-FINDING METHODS

| AUTHORS  | INSTITUTION                                 | NUMBER OF OBSTETRIC PATIENTS | PER CENT WARD OR CHARITY PATIENTS | NUMBER OF CASES OF TUBERCULOSIS | INCIDENCE OF TUBERCULOSIS (PER CENT) |
|--|---|------------------------------|-----------------------------------|---------------------------------|--------------------------------------|
| Allen and Bauer <sup>7</sup><br>Chicago, Ill.                | Rush Home Service and Presbyterian Hospital | 9,696                        | -                                 | 7                               | 0.07                                 |
| Fox <sup>8</sup><br>Oak Park, Ill.                           | West Suburban Hospital                      | 7,628                        |                                   | 11                              | 0.14                                 |
| Kushner <sup>9, 10</sup><br>New York                         | Bronx Hospital                              | 3,166                        | 100%                              | 0                               | 0.00                                 |
| Levine and War-<br>rick <sup>11, 12</sup><br>Brooklyn, N. Y. | Beth El Hospital                            | 13,600                       | 33                                | 1                               | 0.01                                 |
| Potter <sup>13</sup><br>Orange, N. J.                        | Orange Memorial Hospital                    | 10,000                       | 23                                | 3                               | 0.03                                 |
| Tamis and<br>Clahr <sup>14</sup><br>New York                 | Morrisania Hospital                         | 1,009                        | 100                               | 0                               | 0.00                                 |
| Tisdall <sup>15</sup><br>Brooklyn, N. Y.                     | St. Catherine Hospi-<br>tal                 | 19,634                       | 15                                | 15                              | 0.08                                 |
| Tucker <sup>16</sup><br>Chicago, Ill.                        | Chicago Maternity<br>Center                 | 17,739                       | 100                               | 18*                             | 0.10*                                |
| Total  |   | 82,472                       |                                   | 55                              | 0.067                                |

\*The 18 cases of Tucker include 8 cases in which tuberculosis was suspected but not proved due to the patients failing to return.

The data of Royston, Jensen and Hauptman<sup>17</sup> (St. Louis Maternity Hospital and O.P.D.) are omitted from the table. Some of their patients (number not stated) were referred to them for delivery because of known tuberculosis, and the authors point out that their figures therefore do not represent a true incidence of tuberculosis. Of 13,570 patients, 51, or 0.37 per cent, had tuberculosis. Of the patients with tuberculosis, 37 per cent were negroes.

incidence of unsuspected tuberculosis discovered by routine fluoroscopy. There was a striking similarity in the two figures, 0.87 per cent for unsuspected syphilis and 1.06 per cent for unsuspected tuberculosis. In the present study, a similar investigation reveals a surprising change. Although the incidence of tuberculosis remains essentially the same (1.06 and 0.96 per cent), the incidence of unsuspected syphilis has dropped to a little more than one-third of its former level (0.87 to 0.3 per cent). This is shown graphically in Fig. 3. The incidence of known syphilis increased slightly (0.62 to 0.73 per cent). There is a plausible explanation for this dramatic decline in unsuspected syphilis. On July 1, 1937, the Illinois hygienic marriage law became effective, requiring, among other things, premarital serologic tests for syphilis. From July 1, 1937, to Jan. 1, 1941, a total of 189,846 blood specimens have been tested in the Illinois State Diagnostic Laboratories in compliance with this law. Of this number, 2,615, or over 1.3 per cent, were positive.<sup>18</sup> (These figures do not take into account the tests done in private laboratories.)

With such highly satisfactory results accruing from large scale syphilis case-finding activities, is it not reasonable to expect an equally

The incidence of unsuspected tuberculosis of clinical importance discovered by this survey has remained nearly the same during the second period (0.96 per cent) as it was in the first reported period (1.06 per cent). The slight decrease of 0.1 per cent may well be attributed to statistical limitations. However, a factor was operating which would tend to decrease the incidence, namely, the dilution of the fluoroscoped group by the ever-increasing number of re-examinations of healthy subjects during recurring pregnancies. That is, during each year that the program operates, there is included a progressively increasing number of women who have been found by fluoroscopy to be free of clinical tuberculosis in previous pregnancies. (Those discovered to have tuberculosis are included in the group of known cases in any subsequent pregnancies.) During the calendar year of 1940, 18.6 per cent of the women fluoroscoped had been examined by us in one or more prior pregnancies. We conservatively estimate that during the second period of the survey, 10 per cent of the 6,928 women examined were repeaters. If these 693 were deducted from the total, the incidence of unsuspected tuberculosis would be 1.07 per cent, a figure essentially identical to that of the first period.

#### DISCUSSION

What is the significance of discovering that approximately 1 per cent of our prenatal patients have unsuspected clinically important tuberculosis? As a means of estimating the value of the present case-finding program, we have compared our data with the incidence of tuberculosis in pregnant patients reported from several hospitals and maternity centers where tuberculosis case-finding programs were not employed. The social and economic status of the patients in most of these groups appears to be equal to or lower than that of the patients in our series. These data are summarized in Table II. In 82,472 obstetric patients, only 55 were found to have tuberculosis, an incidence of 0.067 per cent. The 1 per cent unsuspected tuberculosis discovered in our patients by routine fluoroscopy represents an incidence 15 times greater.\* It is even more striking that the incidence of *active tuberculosis* found in our survey is *ten times greater* than that found in similar groups where case-finding methods were not used. It is therefore a fair inference that 90 per cent of all active tuberculosis is missed by not employing some effective case-finding program. Where else in medicine is a 90 per cent diagnostic error tolerated when simple, adequate methods are available for elimination of the error?

Routine serologic tests for syphilis in pregnant women have come to be regarded as a medical necessity, and in some states as a legal necessity. Today, no one questions the wisdom of this procedure. In our first report,<sup>6</sup> we compared the incidence of unsuspected syphilis discovered in the prenatal clinic by routine Wassermann and Kahn tests with the

\*In our series, there were 99 additional patients with known tuberculosis.

Thus, it is also at a time when appropriate treatment will be of great benefit. Second, exposure of the new-born infant may be prevented by isolation from the mother in cases where the sputum contains tubercle bacilli.

Jameson<sup>20</sup> has proposed that the funds spent on prenatal case finding could be used to better advantage in providing superior obstetric and medical care for the tuberculous pregnant woman, preferably in institutions organized especially for this purpose. It should be emphasized that all too often, even in the great majority of cases, the tuberculous pregnant woman is not recognized as such unless special case-finding methods are used, and therefore she cannot benefit by the special medical care proposed.

Much discussion and controversy have raged concerning the relative merits of various case-finding techniques. We believe that in the hands of well-trained personnel, chest fluoroscopy followed by roentgenograms in suspected cases is an inexpensive, accurate, and efficient method.

As Bloch<sup>19</sup> has said, "There is good reason to believe that very few of even small parenchymal infiltrations are overlooked by an experienced examiner who is well trained in fluoroscopic technique, in roentgen diagnosis, and in pulmonary pathology. Most of the critics of the fluoroscopic method with whom we have had personal contact betrayed a considerable lack of these requirements and offered opinions on the subject which originated either from hearsay or from an apprehension of the unknown."

Many of the figures cited to discredit the fluoroscopic method<sup>21</sup> include in the percentage error instances in which insufficient diagnoses were made as well as instances in which lesions were erroneously diagnosed by fluoroscopy, and subsequently disproved by roentgenograms. Such criticisms are misleading in that these latter errors are quite inconsequential, for their inclusion does not reduce the total amount of tuberculosis discovered in the group.

The studies of Israel and Hetherington<sup>22</sup> are noteworthy. In a series of 1,021 subjects examined simultaneously by fluoroscopy and stereoscopic roentgenograms, in only 4 among 211 cases of definite tuberculosis found by x-ray were tuberculous infiltrations of immediate clinical significance missed by fluoroscopy. They calculated that the accuracy of fluoroscopy was 99 per cent in the hands of experienced physicians and 96 per cent in the hands of physicians less well trained. Stiehm<sup>23</sup> believes that fluoroscopy has certain definite advantages over roentgenograms, and reports instances of fluoroscopy discovering lesions missed on stereoscopic films.

A large part of the criticism directed against fluoroscopy as a screening method is directed against the use of fluoroscopy alone (without roentgenograms of suspected lesions). With this we have no quarrel,

satisfying decrease in the incidence of tuberculosis among prenatal patients if similar laws were applied to tuberculosis case finding? Just as the discovery of syphilis before marriage protects the innocent partner as well as the offspring against syphilis, so would premarital detection of tuberculosis protect the family.

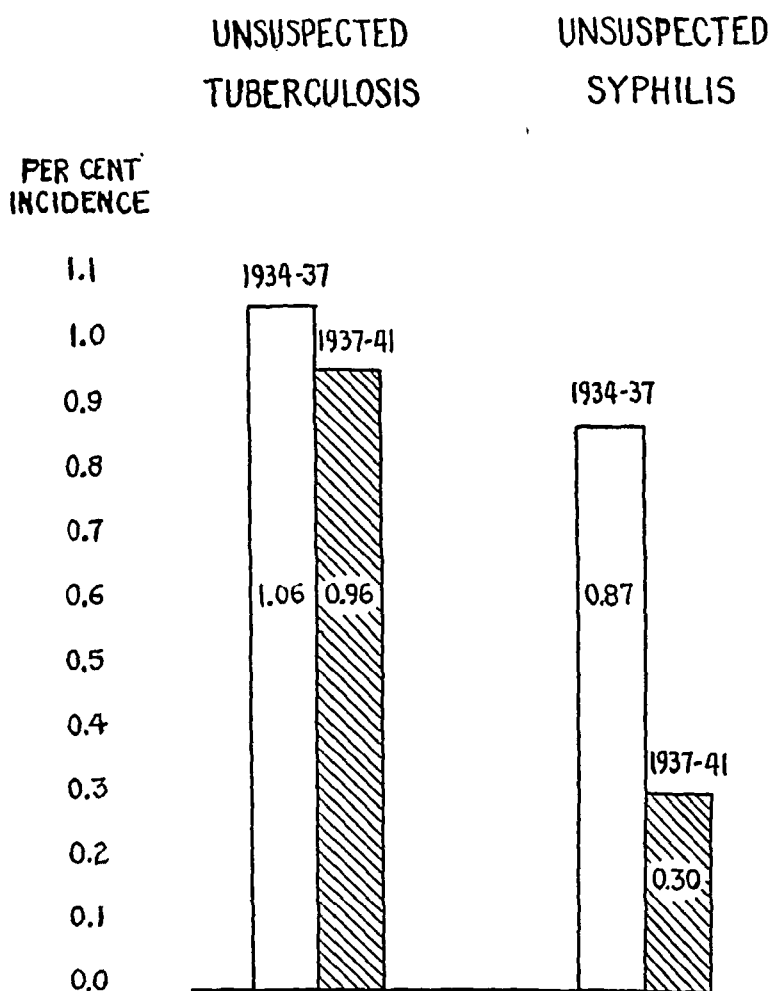


Fig. 3.—Comparison of incidence of unsuspected tuberculosis and of unsuspected syphilis in pregnant women, in the periods 1934 to 1937 and 1937 to 1941. The slight decline in the incidence of unsuspected tuberculosis in the two periods is in contrast with the marked decline in the incidence of unsuspected syphilis, following the passage of the Illinois hygienic marriage law in 1937.

“Case-finding has become the watchword in the fight against tuberculosis.”<sup>19</sup> Recent years have seen constantly increasing activity in this field, especially among the adult population. It would seem that there is not a group anywhere more appropriate for the application of tuberculosis case finding than obstetric patients, for here the rewards of one’s efforts are magnified. In the first place, the disease is discovered at a time when the human organism is undergoing an unusual strain and therefore at a time when the disease is most dangerous to the patient.

on 1,425 pregnant women, using the single "middle dose" tuberculin screen. Of the 671 patients who were tuberculin-negative, there were two cases of active tuberculosis, and among the 144 patients who failed to return to have the test read, there were two additional active cases.\*

Tuberculosis case-finding programs for prenatal patients have been restricted almost exclusively to clinic patients. In view of the increased danger from tuberculosis during pregnancy, and since patients in the upper income brackets are not immune to the disease, it would seem desirable that private obstetric patients also should have the benefits of modern case-finding methods. In private practice, the use of routine roentgenograms probably is the most feasible method. That such a program is actually workable and productive of worth-while results has been demonstrated by Graham.<sup>29</sup> Routine roentgenograms made on 800 consecutive private obstetric patients revealed 8 cases (1.0 per cent) of active tuberculosis and 24 cases (3.0 per cent) of other significant parenchymal disease.

Lest we be lulled by a false sense of security engendered by the marked decline in the tuberculosis death rate which our generation has seen, it is noteworthy that this decline is not shared equally by all age and sex groups. Wolff's study<sup>30</sup> of the differential decline of the tuberculosis death rate in various age and sex groups shows a striking lack of decline in the group of young adult females. As the general tuberculosis death rate decline is worldwide, so also the retarded or absent decline for young adult females is worldwide. In some countries, notably England, there has been a real increase in the mortality in this group.† Wolff suggests that this failure of young adult females to share in the favorable general mortality statistics is closely connected with childbearing and maternal activity. "Hence, it is our future task to diminish further the great risk of young women from tuberculosis mortality during the years of increased generative and maternal activity. This task is a medical one not to be solved by preventing pregnancies in young women, but by alleviating the dangers always connected with childbearing. . . ."

Tuberculosis has moved from first place to seventh place as a cause of death in the general population. But for young women of the child-

\*Graham, Auston and Putnam<sup>27</sup> x-rayed and tuberculin-tested 7,493 individuals in Alabama, and Savard, Putnam and Opie<sup>28</sup> 1,389 in Jamaica. Among the 8,882 individuals, 2.43 per cent manifest tuberculosis was found, the incidence being 3.14 per cent in positive reactors and 0.35 per cent in nonreactors. Including also tuberculosis found on x-ray without symptoms, the incidence of combined manifest and latent apical tuberculosis was 4.89 per cent, or 6.35 per cent among positive-reactors and 0.66 per cent among nonreactors. Thus there is about 10 times as much tuberculosis, both manifest and latent, among positive as among negative reactors to tuberculin, and an appreciable number of cases of tuberculosis of clinical importance would have been missed by x-raying only positive-reactors. The first group of authors state (p. 138): "*the tuberculin tests did not reveal all persons with demonstrable x-ray lesions, a few of which were manifest. Consequently any final discussion of the amount and character of tuberculous infection . . . should take into consideration the results of both tuberculin tests and x-ray examinations*" (italics ours).

†During the war years of 1939 and 1940, the death rate from tuberculosis in England and Wales for the population as a whole increased 9.7 per cent over that in former years, and the highest rate of increase, 15 per cent, occurred in females between the ages of fifteen and twenty-five, a group which already had the highest rate.<sup>31</sup>

except that in some instances a clear distinction is not made as to which method is being criticized.

Roentgenograms offer the advantage of a permanent record and of some increase in accuracy, but in many situations it is doubtful that the slight increase in accuracy per se justifies the greatly increased expense. The several miniature roentgenographic methods recently introduced probably sacrifice accuracy to a point where it is equal to, or below, the level of accuracy of the fluoroscopic method.

There would appear to be a number of reasons why the tuberculin survey method is not as suitable for case finding in the average adult group as the various roentgenologic methods. The tuberculin method is considerably more cumbersome, in that it requires multiple visits of each patient. It has been found that numerous adult patients tested do not return for the reading of the tests, and considerable personnel is necessary for adequate follow-up work. Ianne and Muir,<sup>24</sup> for example, found that of 805 prenatal patients given tuberculin tests, 114 (14 per cent) failed to return for a reading, and of the 284 positive reactors, 32 (11 per cent) failed to return for roentgenograms. Douglas and Birkelo<sup>25</sup> found that of 1,425 prenatal patients given tuberculin tests, 144 (10.1 per cent) failed to return for the test to be read.\* A second disadvantage of tuberculin surveys in adult groups, especially in metropolitan areas, is the large percentage of positive reactors, all of whom require roentgenograms. In Ianne and Muir's<sup>24</sup> prenatal patients (Santa Clara County Hospital, San Jose, California), 41.4 per cent were positive reactors to tuberculin, and in Douglas and Birkelo's<sup>25</sup> study (Prenatal Clinics of the Health Department, Detroit), 47.6 per cent reacted to tuberculin. Inasmuch as all positive reactors require roentgenograms, the cost of these added to the expense already incurred in tuberculin testing would make the total expense closely approach that of a survey using roentgenograms from the beginning. In contrast to the large percentage of roentgenograms required in tuberculin surveys, in our fluoroscopic survey, roentgenograms were made on only 3.5 per cent of the subjects. The fluoroscopic method has the great advantage of scheduling the complete examination for tuberculosis at the time of the first clinic visit, thus eliminating follow-up failures and expense.

A further objection to the tuberculin method for adults is raised by the question of accuracy. In a study correlating the tuberculin test and roentgenograms, Crimm, Potts and Hudson<sup>26</sup> found that "about 21 per cent of the individuals with pulmonary lesions would have been overlooked" if the tuberculin test alone had been employed. Douglas and Birkelo<sup>25</sup> made simultaneous tuberculin tests and roentgenograms

\*Of the 10,968 fluoroscoped patients in our series, 33 (0.3 per cent of entire series, 9 per cent of x-rays ordered) failed to have the x-rays ordered at fluoroscopy. About half of these did not return for further prenatal or obstetric care. This leak has now been stopped by completing the examination, including roentgenograms, at the first visit.



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## PROGRESS IN MYOMECTOMY\*

### SURGICAL MEASURES AND DIAGNOSTIC AIDS FAVORING LOWER MORBIDITY AND MORTALITY

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THE operation of myomectomy was devised a little over one hundred years ago. According to Noble,<sup>1</sup> 1906, the earliest operations for the removal of fibroid tumors of the uterus were myomectomies. The first deliberate removal of a fibroid tumor was performed by Amussat in 1840. Amussat's work was not fruitful, as those who imitated him in France had bad results, and the operation was soon abandoned in Paris. W. L. Atlee<sup>1</sup> was the next surgeon to perform a myomectomy, which was the first successful one on record. Atlee's first operation by the vaginal route was performed in 1845.

According to Bonney,<sup>2</sup> myomectomy, in the early experience with this operation, consisted for the most part in removing pedunculated tumors. Only later experience gave gynecologists the courage to remove fibroids

\*Read (by invitation) at a meeting of the Brooklyn Gynecological Society, March 6, 1942.

*bearing age, tuberculosis is still first as a cause of death.* The tuberculosis toll of this group accounts for 20 per cent of all deaths, twice as high a mortality as from all puerperal causes.<sup>32</sup> In the light of these facts, a roentgenologic case-finding method becomes an essential part of prenatal care.

#### SUMMARY AND CONCLUSIONS

1. The inadequacy of symptoms and physical examinations as means of discovering pulmonary tuberculosis has been discussed. An error of 90 per cent may be expected when these methods alone are used.

2. Routine chest fluoroscopy, followed by roentgenograms in all cases with definite or suspected lung pathology, is a satisfactory method of finding tuberculosis when carried out by an experienced examiner trained in fluoroscopic technique and lung pathology.

3. Application of this method to 10,968 pregnant women, unselected except for the exclusion of known tuberculosis, disclosed 110 cases of unsuspected clinically important tuberculosis, or an incidence of 1.0 per cent. Seventy-four cases, or 0.7 per cent, were shown to be active during the pregnancy.

4. The incidence of unsuspected tuberculosis has remained nearly the same for the two periods of this investigation, namely, 1.06 per cent during 1934 to 1937 and 0.96 per cent during 1937 to 1941.

5. In contrast to this, the incidence of unsuspected syphilis declined markedly, from 0.87 per cent during 1934 to 1937 to 0.30 per cent during 1937 to 1941. This decline may be attributed to the passage of the Illinois hygienic marriage law in 1937.

6. Routine chest roentgenologic examinations should rank with routine Wassermann tests as a medical necessity in pregnant women. The desirability of premarital laws relating to tuberculosis similar to those relating to syphilis has been discussed.

7. Tuberculosis in pregnant women is still an important problem, for although it has declined from first to seventh place as a cause of death in the general population, it still remains as the leading cause of death for women of the child-bearing age. The tuberculosis toll in this age-sex group accounts for 20 per cent of all deaths, twice as high a mortality as from all puerperal causes.

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In many cases hysterectomy has been performed where myomectomy would have been feasible. On numerous occasions I have been able to demonstrate upon the extirpated myomatous uterus that the fibroids could have been enucleated satisfactorily, leaving the organ intact. Careful inspection and palpation of the myomatous uterus in situ can well reward surgeon and patient for the few moments spent in determining the possibility of doing the more conservative operation. The surgeon's interest in the special task and his sympathetic attitude toward conservatism are essential prerequisites to the technical problem at hand. This is undoubtedly as important in performing myomectomy as in any other plastic reconstruction of organs and tissues.

Still another reason it has seemed to me for a lessened interest in acquiring familiarity with measures designed to conserve the reproductive function in women, is the expeditious manner in which hysterectomy may be carried out in accordance with accepted technical standards. The experienced gynecologist who is especially interested in retaining the uterus will, however, go to the extreme pains, as Counsellor<sup>6</sup> has done, of conserving menstrual function, though it becomes necessary to anastomose the body of the uterus with the lower portion of the cervix after removing part of the uterus occupied by a cervical fibroid. I have several times removed large intraligamentous fibroids and sub-cervical fibroids, leaving the uterus intact with conservation of menstruation and, occasionally, of reproduction.

Myomectomy is not feasible under three circumstances:

1. When the adnexa are hopelessly diseased and a plastic reconstruction of the Fallopian tubes is impossible, the ovaries being in such bad condition through chronic inflammation or endometriosis as to contraindicate partial resection.
2. When malignancy, especially carcinoma, is present.
3. When there are adenomyomas which cannot be shelled out without sacrificing too much of the myometrium.

Myomectomy may be said to be indicated chiefly in the childbearing age (1) to conserve the possibility of reproduction, and (2) to conserve menstruation.

The painful experience encountered by most gynecologists who have had to do a hysterectomy for fibroids in a young woman, particularly one who has never borne a child, will not fail to make them consider carefully the feasibility of doing a myomectomy whenever it is possible.

In general, nulliparous women under 40 years of age, who are to be operated upon for fibromyomas, may be offered the choice of a myomectomy with the proviso that it may not be possible to carry it out successfully. When no children are desired, an attempt can be made to conserve the uterus for menstruation and endocrine balance, particularly in the neuropathic patient, provided the adnexa are found to be in good condition. Formerly myomectomy was considered only in relatively

having "shorter and shorter pedicles until at last they assayed to cope with those having none at all."

Bonney refers to W. Alexander of Liverpool, who reported in 1898, on a technique by which he had been able to remove successfully as many as twenty-five tumors from a single uterus. Alexander's paper met with hostile reception and nobody apparently referred to it until 1922 when Bonney looked up the literature on the subject.

The fuller development of myomectomy may be said to have taken place in the last three decades. Chief among its protagonists are Howard A. Kelly, C. P. Noble, and the Mayos in America and Victor Bonney in England. In 1922 William J. Mayo<sup>3</sup> could report upon 909 cases while Bonney in 1925 reported the results of 220 consecutive myomectomies. Both Mayos and Bonney have since reported on larger series. Counsellor and Bedard<sup>4</sup> in 1938 reported on 523 additional cases from the Mayo Clinic while Bonney had done 403 myomectomies by 1930. Several reports dealing with 100 or more consecutive operations for uterine fibroids have been found in recent literature. But by and large there appears still to be hesitation on the part of gynecologists and more especially of general surgeons who prefer hysterectomy to myomectomy, reserving the latter for isolated cases.

The slow development of myomectomy as compared with other standard abdominal operations was stressed by Bonney as recently as 1931, when he discussed its technique. The most important objection leveled against this operation was hemorrhage, which was believed to render it more dangerous than hysterectomy.

Many gynecologists can look back upon the earliest experience with myomectomy in the period between 1905 and 1925, when hemorrhage was considerable, at times alarming, and shock was not uncommon. Too tight and massive suturing to control bleeding was followed by pressure necrosis and marked febrile and peritoneal reactions. The post-operative convalescence was further handicapped by intestinal distention and vomiting which added to the morbidity and in some instances to mortality. For these reasons many gynecologists and most general surgeons were led to prefer hysterectomy for the removal of fibroids as the more satisfactory procedure.

There is another reason which may account for the unpopularity of myomectomy. The matter of conserving genital function was apparently negligible in the early decade of this century; it was still the era of removing ovaries for the slightest pathologic indication. Credit is due Howard A. Kelly<sup>5</sup> and William J. Mayo for having urged the importance of conserving both reproductive and menstrual function for women in the third and fourth decades of life.

Since Mayo's recommendation, the operation of myomectomy has appeared to gain in popularity. But this has followed the tendency toward surgical conservatism in general, especially with regard to the ovaries. Perhaps to some extent the advances made in the study of different aspects of sterility and of endocrine function may account for renewed interest in myomectomy.

It has been demonstrated by hormonal assays that in the normal menstrual ovulation cycle there is an increase of female sex hormone at about the time of ovulation and again a few days before the next menses. Immediately after the onset of the menses an abrupt drop regularly takes place. The ovaries, however, continue to function even when the uterus has been removed and the blood cycle is not abolished.

Malignant changes of myomas occur in from 2 to 4 per cent of cases. Examination of fragments of the fibroids by frozen section can be resorted to before closing the abdomen when one of the tumors is at all suspicious. If the pathologic diagnosis is not conclusive, hysterectomy may be deferred until more complete histologic studies have been made of the tumors or at once be carried out without waiting for the laboratory report. Should the laboratory findings determine malignancy one may resort to the use of x-ray or radium.

Sarcoma can at best only be conjectured preoperatively. During the operation it will not often be possible to recognize its presence by inspection. When opportunity has been afforded to observe the progress of the growth which is rapid, sarcoma will naturally be strongly suspected. A very fleshy tumor, showing degenerative changes, provokes suspicion of its malignant character. In such cases a frozen section can give the desired information.

Should the diagnosis of sarcoma be made positively it will then be necessary to consider its size, its removability, the patient's age, her parity, and, in case of sterility, her keenness for childbirth. In a young woman who has borne no children, one can take the risk of removing the tumors and treat them as fibroids, keeping careful watch in the future. If there should be any signs of activity or tendency to rapid growth, resort to x-ray therapy can obviate an operative intervention with complete satisfaction because sarcomatous degeneration of fibroids is entirely amenable to x-ray therapy. On the other hand, hysterectomy can be done if this should be considered preferable.

Sarcoma has been encountered five times out of 481 myomectomies in the cases at Mt. Sinai Hospital. In all 5, the tumor was relatively small and was discovered by the routine examination in the pathologic laboratory. Two were spindle-celled sarcoma and three myosarcoma. Three patients became pregnant and have shown no tendency to recurrence. In several instances frozen section showed marked cellularity without atypical mitosis. Careful follow-up in such cases is essential.

Hilliard Miller<sup>7</sup> has recently made a plea for myomectomy in women between 20 and 40 years. In 141 myomectomies he found microscopic sarcoma in three specimens. Greenhill<sup>7</sup> remarks editorially in connection with Miller's report that removal is nearly always curative without need of postoperative irradiation and that it is rare for recurrences to manifest themselves after such sarcomas.

young women. There appears to be a growing tendency in all parts of the world to extend the operative indication beyond the fortieth year. The age limit has been raised by some gynecologists to 45 years.

With few exceptions, myomectomy is confined to the period of reproduction. Beyond this period of life it is infrequently encountered. Less than 5 per cent were met in 481 cases of myomectomy at Mt. Sinai Hospital in women over fifty years of age (Table I); 14 between 50 and 60, i.e., 3.9 per cent; 5 cases between 60 and 69, i.e., 1 per cent. Only 12 myomectomies were done after the menopause. The earlier in the childbearing age fibroids are encountered, the more ideal is the operation of myomectomy.

TABLE I. AGE DISTRIBUTION OF 481 MYOMECTOMIES

|             |     |
|-------------|-----|
| 20-29 years | 127 |
| 30-39 years | 299 |
| 40-49 years | 36  |
| 50-59 years | 14  |
| 60-69 years | 5   |

It will be seen from this table that 426 myomectomies were done between the twentieth and fortieth years (88.5 per cent).

Exceptionally girls under 20 may develop one or several or more fibroids. Bonney had an extraordinary case of a girl of 19 from whom he removed 92 fibroids. The chances for developing new fibroids in such case must be considerable, first because of the long period of years left to her and second, as Bonney has remarked, because the disposition to grow more fibroids must be peculiarly inherent.

Although the incidence of first pregnancies in the fifth decade is not large, it is sometimes of the greatest importance to a newly married woman of 40 or over, who, despite having fibroids, continues to menstruate and, therefore, hopes for a child.

It is noteworthy that of the 481 patients in whom myomectomy was done, 224, or 42 per cent, had never conceived and 88 patients had had one child; 39 had two children. The rest had three or more children. In the whole group the total number of children born was 362. Of those who were gravid at some time, 58 had had one miscarriage, and 24 had had two miscarriages; the rest had had from 3 to 5 miscarriages. The total number of miscarriages was 116, or one to three of pregnancies at term.

That myomas actually play a role in the production of sterility has been proved repeatedly by pregnancy which follows enucleation of the tumors. Twenty-five of the 481 patients were pregnant at the time of myomectomy in the material of the Mt. Sinai Hospital; 13 of these went on to full term.

The ovarian cycle and its secondary menstrual cycle are essential during the period of reproduction, not only for childbearing but also for health, being an important link in the chain of endocrine function.

ity was 2.8 per cent. My own series as a subgroup consisted of 394 hysterectomies (10.6 per cent of the total series) and 171 myomectomies (35.2 per cent) of the total number of myomectomies. There was in my personal cases a mortality of 2.35 per cent in the 394 hysterectomies and no deaths in 171 myomectomies. Recent results from myomectomy compare favorably with the best results from hysterectomy.

The associated adnexal lesions for which hysterectomy is done expose the patient to greater risk. Myomectomy is as a rule a clean procedure and as such should not entail the same hazard.

The danger of embolism in my experience does not enter into these cases to any greater extent than in the ordinary laparotomy. There was one fatal embolism in the 481 cases at Mt. Sinai Hospital.

The morbidity of all cases, using the American College of Surgeons' standard, i.e., a rise to 100.4° F. on any two days excluding the day of operation varies in different statistics. Two hundred sixty-five patients out of the 481 myomectomies had some elevation of temperature for five days; 189 had some elevation for ten days; 26 patients had some fever beyond the fourteenth day.

Although the temperature reaction is a definite index of the postoperative course following myomectomy as of any other operation, it does not have the same importance as vomiting, intestinal distress, wound healing, general discomfort or comfort, effect on the circulation and kidneys, and the duration of the hospital stay.

The duration and course of convalescence are the best practical index to the postoperative recovery. Four hundred and thirty-one of the 481 patients left the hospital within three weeks; 50 patients were hospitalized for more than three weeks. I have no comparative statistics on this point with respect to hysterectomy, but if the latter should be shown to entail a shorter period of hospitalization it would not negate the value of myomectomy for which the additional week or two is more than offset by the value of an intact uterus. My present impression is that myomectomy compares favorably with, and in many cases is followed by a greater degree of comfort to the patient, than hysterectomy.

What to tell the patient before undertaking a myomectomy is of importance. The only proper statement seems to be that one can and will do his best to conserve the uterus in attempting to remove the tumors; but that it is not possible to guarantee that myomectomy will be feasible and that hysterectomy may not prove most advisable in the end. Occasionally, after a survey of the laparotomy findings, one may consider it worth while to discuss the situation with an intelligent husband in case a general anesthetic is employed or with the patient herself in case spinal analgesia is employed. I have had occasion to resort to both these procedures.

*Technical Considerations.*—In reviewing early experiences with myomectomy several factors were found to account for the unfavorable results formerly encountered. (1) It was common practice to cut away a

Carcinoma may be associated with fibroids. In a series of 188 cases, Bland found carcinoma of the cervix twice and of the body eleven times. In the 481 cases of myomectomy of the present report there was not a single carcinoma. The reason for this absence is difficult to explain except in the possible peculiar immunity to cervical carcinoma enjoyed by the patients in the material from Mt. Sinai Hospital. On the other hand fundal carcinoma is by no means rare. Perhaps the uterine cavity was not entered in a sufficient number of cases to discover fundal carcinoma. Nevertheless there was not a case encountered in the follow-up.

The question of malignant disease associating with fibroids frequently comes to the foreground. Carcinoma apparently does not develop in the myoma per se. If present in the myomatous uterus, it arises from the cervix or the endometrium. When found, it demands total hysterectomy with radiotherapy or radiotherapy alone. It should never escape diagnosis, because curettage and biopsy of the cervix may be relied upon to establish its presence in suspected cases. Although not encountered in the Mt. Sinai Hospital series, uterine carcinoma has been found associated with fibroids in from 1:2 to 3:4 per cent of cases reported in the literature. It should therefore always be kept in mind.

In connection with the diagnosis of carcinoma it is possible in most cases to demonstrate its presence or absence by injecting a viscous soluble x-ray opaque solution into the uterine cavity.<sup>8</sup> For this purpose only 2 or 3 c.c. of the contrast medium are used, the outlines of the growth being visualized without the danger or the necessity of the fluid entering the peritoneal cavity. This method may be used as a routine preliminary step in cases where myomectomy is contemplated and carcinoma is even mildly suspected. The method may precede exploratory curettage which it may render unnecessary.

Mortality following myomectomy was appreciable in the beginning of the present century. Five per cent mortality was regarded as favorable. Higher rates were not infrequent.

The more recent statistics show considerable improvement. Counseller and Bedard<sup>4</sup> reported a mortality of 1.14 per cent in a series of 523 myomectomies between 1925 and 1934. Hamant,<sup>9</sup> in 1933, reported one death in 156 myomectomies. Hilliard Miller had one death in 141 cases. The operative mortality of myomectomy need be no greater than that of hysterectomy, i.e., between 1 and 2 per cent.

There have been 9 deaths (1.9 per cent) in a series of 481 myomectomies performed between Jan. 1, 1922, and Dec. 31, 1941, at Mt. Sinai Hospital distributed among 47 operators; 13 were members of the Attending Staff; 25 were on the Resident Staff; and 9 were general surgeons.

There were 3,696 hysterectomies done by the group of 47 operators at Mt. Sinai Hospital during the same period. The total average mortal-



proximation to avoid whitening of the wound edges. Necrosis leads to suppuration, adhesions and eventually intestinal obstruction. A seroserosal suture of the Cushing type is desirable, care being taken not to include the lumen of the interstitial portion of the Fallopian tubes if the latter are encroached upon by the myoma.

The tendency to excise elliptical portions of the seromuscular layers before enucleating the tumors has proved a decided disadvantage. It is better to have a loose flap which can be imbricated, affording close serosal approximation without tension. If necessary, excessive tissue can be trimmed after the nucleation and obliteration of the tumor cavity has been completed. The peripheral sutures may now be tied without undue tension. This procedure allows for wound approximation comparable to the closure of the uterine wound in a cesarean section. Through one incision it is possible to plan the removal of a number of fibroids by squeezing them through the exposed uterine wound and thus visualizing them. When this is not feasible one can locate the tumor, incise it boldly and treat it in the same way as the subserosal intramural tumor at the first attack. If pedunculated tumors are close to either pole of the incision the pedicle can be circumcised and included in the main incision. For multiple subserous tumors it is a good plan to pass a suture to one side of the pedicle cutting it off with due allowance for serosa which can be approximated by the continuation of the preliminary suture.

For securing hemostasis several methods have been employed in my series:

(1) The old method of having an assistant grasp the broad ligaments firmly whenever possible until the fibroids have been enucleated and the suture is complete; (2) clamps protected with rubber tubing are applied to the broad ligaments, utilizing ordinary Carmalt clamps or enterostomy clamps similarly protected. In many cases this was satisfactory. (3) In a number of instances broad tape or stout silk thread was passed by means of a Deschamps needle from the immediate proximity of the lateral wall of the cervix through the broad ligament on each side and tied over its upper margin or just underneath the tube, to avoid the possible cutting through of its lumen. This also was satisfactory in some cases but could not be applied in others where the tumors were large and distorted the broad ligaments or where adhesions made it unfeasible. Whenever possible the uterus may be brought out of the abdominal wound so that the peritoneal cavity can be protected against seepage and at the same time hemostasis more completely secured. (4) The last two and one-half years I have utilized an elastic rubber turniquet passed through the broad ligament from 1 to  $1\frac{1}{2}$  inches outside of the lateral margin of the cervix encircling the cervix on four sides. By stretching the two ends taut posteriorly and crossing them, the ligature is clamped at the constricting point. This has proved the most effective and completely hemostatic method so far devised. I have first tried out this method preliminary to hysterectomy in order to determine how much bleeding was actually occasioned when various portions of the

good part of the myometrium with the fibroid. In other words the incision first made was elliptical, including a good portion of the serosa of the uterus overlying the fibroid as well as part of the muscle wall which was spread over it. The result was that, in approximating the uterine wounds, there was tension which eventually led to necrosis, separation of the uterine wound, suppuration and intestinal adhesions with intestinal obstruction more or less complete. (2) Many wounds were invariably made in order to enucleate individual fibroids. (3) The uterus was replaced into the pelvis with the uterine serosa presenting several or many wounds which provoked agglutination and adhesions. (4) Hemorrhage against which sufficient prophylaxis was not provided. (5) Inclusion of the tubal lumen in the suturing of the uterine wounds which accounted for failure to conserve reproduction.

In the days before transfusion the operation of multiple myomectomy was fraught in many instances with considerable hemorrhage leading to much lowered resistance and shock which was not combated adequately and hence the immediate outcome of the operation as well as ultimate postoperative recovery were often unsatisfactory.

Sometimes the surgeon took the precaution of having an assistant hold the broad ligaments to prevent too much bleeding. Resort to hot pads applied intermittently during the operation controlled hemorrhage to some extent.

The postoperative morbidity and mortality were so much greater than attending hysterectomy and other operations, that most gynecologists and, more especially general surgeons, abandoned myomectomy for the operation of hysterectomy where all the bleeding could be completely controlled.

The problem therefore was threefold: (1) to plan the removal of the tumors in such fashion that they can be enucleated through a minimum of incisions, sometimes one incision sufficing to enable the surgeon to remove several fibroids. (2) The incisions were preferably made on the anterior and superior surface of the uterus, sparing the posterior and posteroinferior aspects as much as possible while keeping a safe distance from the tubal insertions. (3) The incision should be linear and never elliptical, partially bisecting the fibroid so as to determine readily the subcapsular plane of cleavage. Each half of the tumor is grasped with a tenaculum, enabling easy peeling out in an avascular fashion. Blunt and sharp dissection are used. I have found a gauze sponge very handy for the enucleation. Before it is completely enucleated the two halves of the tumor are twisted, thus forming a sort of pedicle which is clamped and cut.

By careful suturing, the cavity left by the enucleated fibroid is obliterated and more or less natural configuration is conserved. Continuous and interrupted sutures may be employed. In suturing the sero-muscular layers care should be given to accurate but not too tight ap-

passing the ligature through a thin avascular portion of the cervix just above the level of the uterocervical junction. Compression of the ureters if this takes place for ten to twenty minutes cannot cause ureter injury. In none of the cases in which the broad ligament cervical tourniquet was used has any injury been encountered.

Of equal importance with the prevention of hemorrhage is the protection of the uterine wounds after the fibroids have been removed. I believe that attention to this matter has saved a good many uteri and has encouraged me to perform myomectomy where I ordinarily would have considered hysterectomy and where the latter operation was advised by colleagues.

Realizing the importance of protecting the uterine wounds, in my early experience I found it serviceable to fix the omentum by fine sutures to the wound area of the uterus or by ventrofixing the uterus to the abdominal wall. Later I employed the anterior edge of the incised vesicouterine peritoneum to cover over most of the uterine wounds, thus at the same time anteverting the uterus and preventing its retrocession into the pelvis. At first the anterior uterine pouch was incised, the peritoneum freed as widely as possible and then sewed to the uppermost angle of the uterine wound. Later I found that it was not necessary to make a flap as in the low flap cesarean section but to tack the intact loose portion of the vesicouterine peritoneum on to the uterus and protect the uterine wounds horizontally. This has been later modified by the equally simple measure of sewing the loose portion of the parietal peritoneum from side to side over and above the upper limit of the uterine incision and completely extraperitonizing the uterine wound area. A portion of the posterosuperior uterine area can thus be segregated from the general peritoneal cavity.

For the low situated posterior uterine wounds, I have employed the appendices epiploicae from the sigmoid or by actually tacking with interrupted fine sutures the sigmoid serosa to the posterior uterine wall. The sigmoid being mobile does not overcome the fixation from above which anteverts the uterus so that in the end the uterus maintains a fairly normal position. When the fibroid is situated at the uterine cornu, the uterine wound may be covered over simply by taking some sutures between the round ligament and the uterine serosa as in the treatment of adnexal pedicles. Both round ligaments may be utilized if the cornual fibroids are bilateral.

In my whole series only one of the early cases had definite symptoms of subacute intestinal obstruction. The uterine wound had not been protected in the manner just described. This patient recovered, thanks to gastric and intestinal drainage and intravenous infusion. In the entire series of 481 myomectomies only one case of postoperative intestinal obstruction required a second laparotomy for the release of a kinked, adherent loop of intestine. This patient recovered.

uterus were incised. In practically all cases where the preliminary test was made incidental to hysterectomy, complete hemostasis was demonstrated. Only when the incision was made into the proximal portion of the isthmus was slight bleeding encountered, but the uterus itself could be incised ad lib without causing any appreciable bleeding. A similar experience was met in myomectomy. The fibroids can be incised bloodlessly, enucleated, and the bed obliterated by appropriate suturing, after which the clamp is removed from the tourniquet and the latter withdrawn. The four openings made by the tourniquet on the anterior and posterior aspects of the broad ligament are then closed by fine catgut sutures which require one or two minutes.

It is a good plan in using this method not to allow the tourniquet to be applied for more than ten minutes at a time because it is theoretically possible that tissue devitalization can take place with the production of histamine which can swarm into the circulation causing possible shock. In one of my first cases from which 33 tumors were removed in this fashion, the elastic ligature was applied for some forty minutes. The patient went into shock after being returned to her bed, and was restored after several hours by intravenous infusion, ephedrine, coramine and cortate medication. There had been no bleeding to account for the shock nor was the operation so long as to consider it a factor in its production. It is quite possible that shock was produced in this case by the prolonged application of the elastic tourniquet. This accident has not been encountered in several dozen myomectomies in which the tourniquet has since been used.

P. Borrás<sup>10</sup> of Rosario, Argentina, has reported well over 100 cases in which he made use of the elastic ligature since our discussing this procedure in 1939, but made no mention of shock. In a personal communication, Borrás expressed the opinion that the shock observed by me in the case in which 33 tumors were removed was due to the length of the operation. With this opinion I do not agree as the length of the operation was one hour and twenty minutes which should not per se induce shock.

The elastic ligature has been used in a number of ways, especially in the early Porro technique. Its use as a cervical uterine vessel tourniquet appears to have been published only comparatively recently by Borrás. Yet the idea may have occurred to others. William Linder of Brooklyn had occasion to use this very method some thirty-odd years ago in a case of fibroids but never published it or followed its use in other cases.\*

It is not suggested that this elastic rubber tourniquet be used in all cases. It is not necessary to employ it for a simple pedunculated fibroid or for small tumors. It is especially indicated where several or more intramural fibroids of good size are to be enucleated and where bleeding can be reasonably certain and considerable. The possibility of injuring the ureter is essentially theoretical. It can absolutely be avoided by

\*Personal communication.

Tubal obstruction can be demonstrated so much more conveniently by uterotubal insufflation with CO<sub>2</sub> that I have not used radiopaque substances for this purpose in myomatous uteri.

The diagnosis of submucous fibroids may be ventured when the patient complains of profuse menses accompanied by clots and cramps. It may be the only fibroid present, enlarging the uterus symmetrically and not beyond the size of a fist. The use of the uterine sound has value in many cases. In past experience an exploratory curettage often disclosed the encroachment upon the uterine cavity, but in a certain percentage even this procedure has failed to establish the diagnosis. We have recently employed x-ray opaque contrast media for this purpose with satisfactory results.

By and large, submucous myomas have heretofore demanded hysterectomy in preference to x-ray treatment or radium therapy. But in young women neither of these radical procedures is absolutely necessary because it can be removed as safely as the ordinary fibromyoma by the vaginal or abdominal route. When solitary it can, except in virgins, be removed by opening the anterior or posterior cul-de-sac. In virgins and nulliparous women, the abdominal route is generally preferable.

Treatment of the submucous fibroid which protrudes from the external os varies with the size and amount of protrusion and the extent of the degeneration and inflammation; also as to whether it is associated with other fibroids requiring removal. If the submucous fibroid is small and protrudes from the external os, it may be treated as a simple polyp by avulsion and in an ambulatory fashion. A larger, apparently uninfected submucous fibroid filling and dilating the vagina may require incision into the remaining portion of the capsule and also removal by avulsion. If the pedicle is long and thick it may be circumcised and ligated before cutting. Sometimes the pedicle is entirely avascular, at other times it may be attended with considerable bleeding.

If bleeding is present after removing the submucous fibroid, the uterine cavity may be packed thoroughly with iodoform gauze. If no bleeding occurs packing is not necessary.

If in addition to intramural and subserous fibroids there is present an infected, degenerated large submucous myoma, it is best to remove the protruding tumor, iodize the uterine cavity and pack it with iodoform gauze which may be left in for one or two days to control bleeding and for purposes of disinfection. The rest of the fibroids may be removed at a later date after all signs of possible peritoneal irritation or inflammation have subsided. It is unwise to attempt abdominal myomectomy at the same operation unless the submucous tumor shows no signs of inflammation.

The incision for a submucous fibroid by the abdominal route is made into the uterine fundus partially bisecting the myoma and grasping each

An important item in prophylaxis of morbidity and mortality in connection with multiple myomectomy is the avoidance of routine appendectomy. It has been a long standing conviction that a quiet, i.e., normal looking appendix should not be removed at the conclusion of a myomectomy because it is so "handy."

One need only to scan the literature and review his own results after laparotomy for pelvic disorders, where an incidental appendectomy was done in order to be convinced that morbidity and mortality are occasionally produced by the appendix stump no matter what the particular technique employed. It is a good rule after performing a complicated hysteromyoplasty to inspect the appendix and to remove it only when adherent or otherwise diseased. Simple myomectomies may be more safely combined with routine appendectomy.

*Ventrofixation and Ventrosuspension as a Precautionary Measure.*—When the incisions have been made on the posterior aspect of the uterus, the latter has a tendency to be anchored down. In order to avoid this the uterus may be ventrofixed by separate plain catgut sutures. Suspension by the round ligaments may also be done. Ventrofixation, moreover, approximates the uterus to the abdominal wall so that if there is any oozing or infection, it may come through the abdominal wound rather than invade the free peritoneal cavity. The fixation produced by plain catgut sutures is temporary and is not likely to interfere with future pregnancies. But this procedure should be reserved for cases where it is chiefly desirable to conserve menstruation.

An idea of the frequency of tubal disease associating fibroids is given by the fact that there were 89 cases out of the 481 cases in which myomectomy was done at Mt. Sinai Hospital. For these lesions unilateral salpingo-oophorectomy was done in 60 cases and partial bilateral salpingo-oophorectomy in 2 cases; unilateral oophorectomy in 3; partial oophorectomy in 9; unilateral salpingectomy in 6 and partial salpingectomy in 2; salpingolysis and salpingostomy in 6. Appendectomy was done in 68 cases; ventrofixation or suspension in 19; hernioplasty in 2; Fothergill operation in 2; and anteroposterior colporrhaphy in 11 cases. Pregnancy was interrupted in 3.

*Lipiodol as a Diagnostic Measure.*—Whenever lipiodol is used for the diagnosis of submucous fibroids or to note the distortion of the uterine cavity by multiple fibroids, the injection should be made very slowly and under fluoroscopic control. As soon as the uterine cavity is filled with lipiodol and before it enters the tubes, the x-ray film can be taken. The pressure should not be raised after the tubouterine junctions have been visualized. The oil should be allowed to escape immediately after the exposure. This precaution is taken to avoid affecting the ciliated epithelium of the tubal lining and to prevent inspissation in the tubal lumen. The use of soluble visco rayopake in fractional doses is superior to the use of lipiodol, because it leaves no residue after a few minutes.

thought that the multiple enucleation would leave a uterus unfit for pregnancy and in the event of conception would be a source of danger. It is, however, surprising how often it may be possible to enucleate most if not all of the fibroids when one starts out with the express object of conserving the uterus. I have removed 33 fibroids from a young woman of 31; and Bonney reports the removal of over 100 fibroids in a single case.

Not all fibroids need to be removed. The large fibroids are always enucleated. In many cases smaller fibroids may be left in situ when their position is in neutral places and their removal might jeopardize the patient's chances for operative recovery.

Multiple enucleations should be attempted unless the technical difficulties are too great, entailing danger per se to the patient. In such cases one may be compelled to do a subtotal hysterectomy or high amputation of the uterus, preserving the menstrual function or, as is the practice in Holland, of transplanting some endometrium in the cervical stump with satisfactory results (Wijsenbeek).\*

There will always be a few cases where some factor arises to prompt the surgeon to leave in one or several small fibroids although it would be preferable to remove them. An anesthetic badly tolerated by the patient or some untoward accident otherwise demanding cessation of further operating may lead the surgeon to a quick decision of concluding the operation as fast as possible. Shock is another consideration. If after removing many fibroids one or two are found on the lower posterior aspect of the uterus the removal of which may demand more time than is required for the simpler removal of fibroids more favorably situated, it is wise not to attempt it. Surgical judgment is tested by just such incidences. It is better under these circumstances to be content with an incomplete removal than with a serious postoperative result.

In Bonney's series of 403 cases the tumors removed were solitary in 166 and multiple in 237.

In 219 cases out of 481 of the Mt. Sinai Hospital series, only one myoma was enucleated. In 262 cases, from 2 to 33 fibroids were removed.

In several cases of young women, myomectomy was followed for ten or more years with normal menstruation and the birth of one or two children before symptoms suggesting new fibroids manifested themselves. The operation of myomectomy may be said in such cases to have earned its own reward. A second myomectomy is rarely done, but in properly selected cases can undoubtedly be repeated. Each case must naturally be treated accordingly. I have recently operated upon a married woman of 40 years, removing multiple fibroids six years after a previous myomectomy done elsewhere. The cervical broad ligament tourniquet made the second myomectomy possible and satisfactory.

\*Verbal communication.

half of the tumor with a tenaculum forceps. By careful dissection the capsule may be freed from the tumor and shelled out, leaving the endometrium intact. The latter is recognized readily by its shimmering bluish appearance and its soft character. The tumor bed is sewn up in the same way as in the case of any intramural fibroid.

Some submucous fibroids, however, are denuded of endometrium over the pole protruding into the free uterine cavity. In such cases the latter must be entered. The mucosa can then be sewn over by submucosal sutures or by sutures which approximate the mucosal edges themselves. Accidental entry into the uterine cavity is treated similarly. If the cervical canal is patulous and no preliminary curettage was done, iodoform gauze can be passed through from above into the vagina using a special gauze passer or ordinary probe. The myometrium is then sewn over in the typical fashion.

Accidental entry into the uterine cavity which can occur in enucleating fibroids that are close to the endometrium need not militate against completion of the myomectomy in favor of hysterectomy. When this accident occurs, the mucosa is sewn with fine catgut as in a cesarean operation. In the 481 cases of myomectomy at Mt. Sinai Hospital, the uterine cavity was opened 57 times. Detailed analysis of these cases showed no appreciable influence on morbidity or mortality. The uterine cavity being clean, it practically always may be opened without adding hazard to the patient. Accidental entry into the uterine cavity, however, was not necessarily due to the presence of submucous myoma.

Submucous fibroids were removed by the vaginal route in 11 cases on the gynecologic service of Mt. Sinai Hospital since 1924. In 2 cases in nulliparous women a small fundal submucous myoma was partially exposed by anterior vaginal hysterotomy and by a single tenaculum hook brought down to a point where it could be incised and shelled out.

The presence of submucous fibroids, in addition to other types, should not discourage attempts at conservative surgery. The interesting case encountered by Dr. H. N. Vineberg in this respect is instructive. In a young woman of 26 he found that he had to cut into the uterine cavity to remove a large submucous fibroid; a number of intramural and subserous fibroids had already been removed. The uterine wounds were all carefully sutured, leaving an organ which differed considerably from the normal nonfibroid-bearing uterus. This patient skipped her next period which should have appeared during her hospital stay and she was duly delivered. Despite the invasion of the uterine cavity, the young impregnated ovum continued to grow to term. As this may have been the only chance this patient had for pregnancy, the surgeon's conservative efforts were abundantly rewarded.

*Multiplicity of Fibroids.*—Formerly, multiple fibroids at once discouraged any attempts at enucleation. As Bonney remarks, it was



The complete planning of myomectomy includes diagnostic measures by which to exclude or demonstrate the presence of intrauterine lesions, chiefly, retained products of conception in incomplete abortion, submucous myoma, polyps, and carcinoma. These can be diagnosed by exploratory curettage done before the myomectomy. Practically all intrauterine lesions are amenable to demonstration by means of radiopaque media injected into the uterine cavity. A viscous soluble crystalloid iodine solution has been found useful and safe and may replace diagnostic curettage. Uterine polyps may be removed by curettage and the polyp forceps, and submucous myomas may be removed by vaginal or abdominal hysterotomy at the same time as other fibroids are removed. If the operation is designed to relieve sterility the uterine incision and suture should guard against implicating the insertion of the Fallopian tubes.

Recurrences are relatively rare and arise from seedling fibroids overlooked at the time of operation or escaping inspection because of their embedded location. The choice of a second myomectomy is left in such cases to the patient, provided she is young enough and still desires children or resort may be had to hysterectomy or radiotherapy. In from 25 to 35 per cent of the cases, myomectomy has been followed by pregnancy. This would appear to justify the pains taken by the surgeon in conserving the uterus.

Myomectomy is the ideal and at present the only conservative treatment for uterine fibroids which preserves menstruation and the possibility of reproduction.

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911 PARK AVENUE

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**Ballon, H. C., and Goldbloom, A.: Serious Injury to the Rectum From Improperly Administered Enemas, *Canad. M. A. J.* 45: 345, 1941.**

A severe injury to the rectum of a 5-year-old child caused by the improper administration of an enema is reported. In reviewing the literature, note is made of 4 cases of severe rectal injury occurring in parturient women. One was produced by an enema three days post partum and the other 3 were injuries caused by enemas given during labor.

CARL P. HUBER.

Recurrent fibroids should be distinguished from polypoid sarcomas which, according to Frank, were doubtless confused by older authors.

The question of recurrence is always properly asked by the patient and considered by the surgeon. Fibroids that have been removed never leave residue from which other fibroids arise. In practically all cases it is safe to say that "recurrences" consist of fibroids that were present at the time of operation which were either overlooked or actually seen but not removed for one reason or other. The new fibroids spring as a rule from seedlings that escaped the eye at the laparotomy or small fibroids which were concealed by their deeply lying sites in the walls of the uterus. In such cases, depending upon the age of the patient and other factors, a second myomectomy may be done, or resort may be had to x-ray or radium. These measures, including secondary hysterectomy should be weighed against successful pregnancies following myomectomy.

#### SUMMARY

Myomectomy was begun a little over one hundred years ago as a bold surgical venture for the removal of a pedunculated tumor which was erroneously believed to spring from the ovary. If there were other similar embedded tumors they were considered inoperable. The operation has gradually developed technically so that today multiple myomectomy is done as a conservative plastic operation upon the uterus with the specific object of not only removing all of the fibroids but of conserving the uterus with retention of menstruation and possible reproduction.

Three dangers attending the operation to an appreciable degree, namely, hemorrhage, postoperative morbidity, and mortality, were gradually reduced by improvements in surgical technique. Hemorrhage has been controlled by temporary constriction of the uterine vessels by the fingers of an assistant, by rubber covered clamps, and finally by use of an elastic rubber tourniquet circumscribing the cervix and constricting the uterine vessels on either side. This elastic tourniquet has made possible the bloodless removal of many fibroids which previously would have indicated hysterectomy.

The reduction of morbidity and mortality was further brought about by careful planning of the uterine incisions which were placed mostly on the anterior and superior surface of the uterus and removing as many fibroids as possible through one incision. By providing adequate peritoneal protection of the wound, covering them with vesicouterine peritoneum, anterior parietal peritoneum, sigmoid epiploica and omentum according to the requirements of the conditions met in the individual cases, intestinal agglutinations, intestinal adhesions, postoperative distress, and morbidity were further reduced. The mortality has been reduced in fairly large series of cases to 1 per cent and below, comparing favorably with the best statistics on hysterectomy.

taken place. This situation has occurred to us in four instances. In two cases a missed abortion resulted while the other two patients went on to full term with no complications and normal babies were delivered.

In summing up the significance of endometrial biopsy as a method for the determination of ovulation, we may say safely that a secretory endometrium is strong evidence that ovulation has occurred, but the finding of a proliferative endometrium does not preclude the possibility of ovulation. Unquestionably, an innocuous method involving daily studies to determine the exact time of ovulation, would be highly desirable.

Within recent years, efforts have been directed toward this objective and numerous methods have been proposed. Claims have been made that ovulation is associated with, and can be diagnosed by, changes in: vaginal pH;<sup>9</sup> bioelectric potential;<sup>10</sup> rectal temperature and basal metabolic rate;<sup>11</sup> oxyhemoglobin determination by the Samuels cycloscope;<sup>12</sup> vaginal smears;<sup>1</sup> and urinary excretion of pregnanediol glucuronidate (P.G.), a metabolic derivative of progesterone.<sup>13</sup> Most of these methods rest on an insecure basis and lack direct confirmation. Two of these procedures, however, appear worthy of more careful consideration. We refer to the vaginal smear method originated by Papanicolaou<sup>14</sup> and extended independently by Shorr<sup>15</sup> and Rubenstein;<sup>1</sup> and the urinary pregnanediol glucuronidate method introduced by Venning and Browne.<sup>13</sup>

We have undertaken a critical study of these two methods with the purpose of correlating the results obtained by these procedures. In the course of this work certain difficulties in the evaluation of ovulation by these methods have arisen. The purpose of this preliminary report is to point out these possible sources of error.

#### PROCEDURE

These studies were made on a large series of women with varying complaints but with no demonstrable pelvic pathology. Patients were instructed in the technique of taking vaginal smears according to the requirements of Shorr<sup>15</sup> and Rubenstein.<sup>1</sup> The smears were taken by the patient and were obtained either with the suction pipette described by Papanicolaou,<sup>14</sup> or by means of a wire loop inserted to the posterior fornix through a speculum. Preliminary results comparing the daily smears obtained with both methods taken in the same patient revealed no significant differences. The smears were stained in accordance with the method of Shorr.<sup>15</sup>

Vaginal smears were evaluated on the following basis: Analysis of estrogenic activity was obtained, using the criteria described by Rubenstein and Duncan.<sup>17</sup> Smears consisting of round cells with relatively large vesicular nuclei (basal or atrophy cells) were assumed to indicate zero estrogen production, while smears consisting of cells with agranular cytoplasm and small pyknotic or fragmented nuclei were assumed to represent maximal estrogen response. Intermediate smears were assigned intermediate values following the scheme of Rubenstein and

## SOURCES OF ERROR IN THE DETECTION OF OVULATION\*

### CORRELATION OF VAGINAL SMEAR STUDIES WITH URINARY PREGNANEDIOL GLUCURONIDATE DETERMINATIONS

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THE detection of ovulation in the human being constitutes one of the fundamental problems in the physiology of reproduction. For a number of years, endometrial biopsy analysis has been the only practical method available for determining whether or not ovulation had occurred in a particular cycle. The basis of this indirect method rests on the assumption that progesterone activity on the endometrium of the uterus is produced by a corpus luteum which can be formed only as a consequence of ovulation. The presence of a premenstrual proliferative endometrium, on the other hand, has been interpreted as indicative of an anovulatory cycle.

However, the assumptions necessary for utilization of this method meet with both theoretical and practical objections which detract from the usefulness of this procedure for the detection of ovulation. The most important of these objections may be listed as follows:

a. Ovulation may occur with a resultant deficient corpus luteum which may secrete amounts of progesterone insufficient to produce a secretory endometrium or the corpus luteum which is formed may be functional for a short period of time. In both cases a premenstrual proliferative endometrium might be found.

b. A corpus luteum may be formed without the liberation of an ovum.

c. The number of biopsies that can be taken in any one cycle is limited, and thus the date of ovulation cannot be determined accurately unless two biopsies are taken relatively close together and reveal first a proliferative and subsequently a secretory endometrium.

d. Clinical experience has long suggested that certain women may ovulate during or near menstruation. Recent studies substantiate these speculations.<sup>1, 2</sup> It is obvious that an incorrect evaluation of ovulation in such a cycle would be likely.

e. According to some investigators, progestational proliferation may be experimentally produced by steroids closely related to progesterone, such as desoxycorticosterone<sup>3-6</sup> and certain of the androgens.<sup>7, 8</sup>

f. A very practical objection to the routine use of endometrial biopsies in the study of sterility problems is the danger that this procedure might be performed during a cycle in which conception has already

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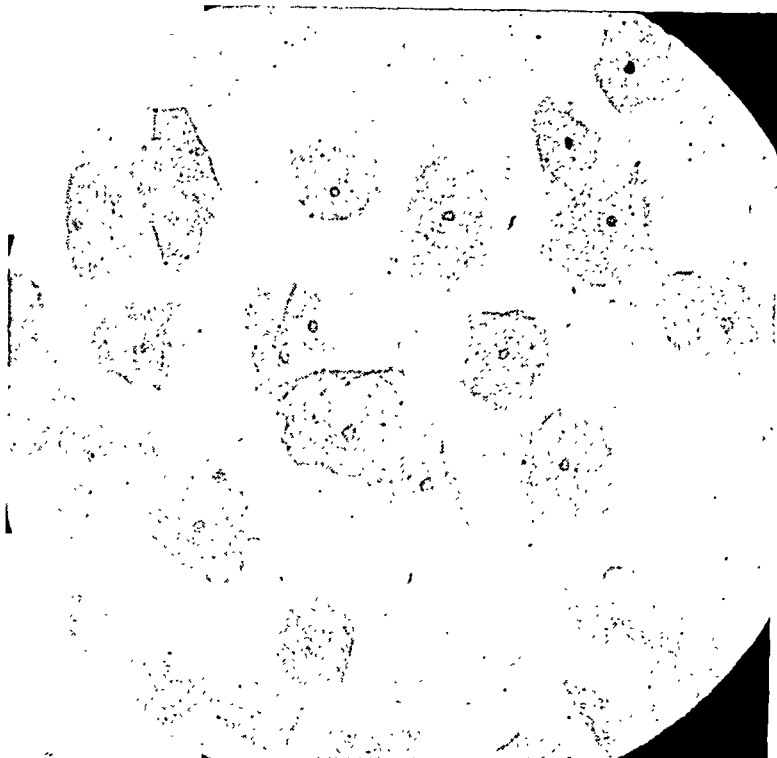


Fig. 2.—A preovulatory smear ( $\times 470$ ), illustrating zero aggregation and minimal folding of the cell edges.

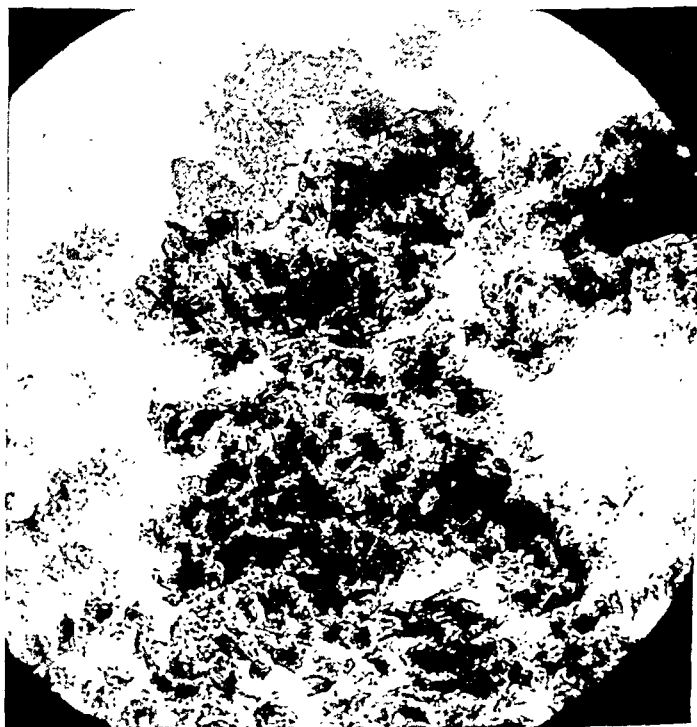


Fig. 3.—A low-power photomicrograph ( $\times 100$ ) of Fig. 1, illustrating marked cell aggregation in a postovulatory vaginal smear.

Duncan. It has been found that the technique of evaluating human vaginal smears for estrogenic activity on this semiquantitative basis, roughly parallels the assay of urinary estrogen excretion.<sup>17</sup> Luteal activity was evaluated both by the degree of desquamation observed in the smear (as evidenced by the folding and aggregation of the epithelial cells) and by the inhibition of cornification due to estrogen. These reactions appear to be the effects of progesterone on the vaginal smear picture.<sup>1, 18</sup> The arbitrary criteria for evaluation of the degree of desquamation used in these studies were as follows:

- 0 Desq.----Aggregation and folding absent.
- 1-plus Desq.----Aggregation absent, but many cells with folded edges.
- 2-plus Desq.----Aggregation absent, most cells edges are folded.
- 3-plus Desq.----Aggregation definite, many cells are folded without being aggregated.
- 4-plus Desq.----Aggregation of most folded cells.

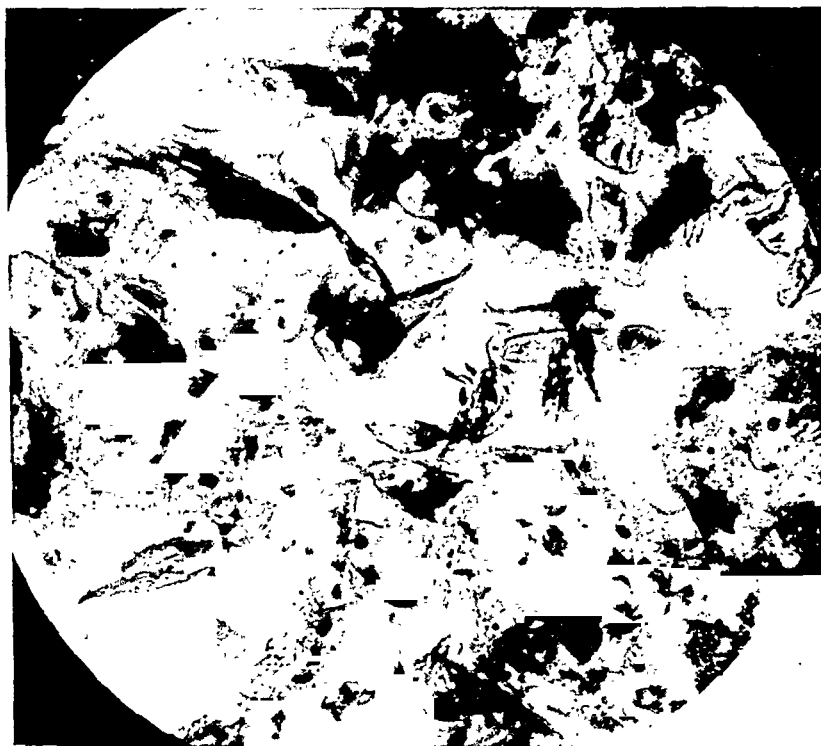


Fig. 1.—A postovulatory smear ( $\times 470$ ), illustrating marked folding of the cell edges.

Figs. 1, 2, 3, and 4 are photomicrographs of vaginal smears illustrating varying degrees of cell cornification and desquamation. The degree of desquamation was correlated with the inhibition of cornification, the composite picture representing roughly progesterone activity. Ovulation, on this basis, was diagnosed by a sharp increase in desquamation index, with a simultaneous decrease from high levels of the cornification index. The evaluation of the degree of cornification, by examination of cytoplasmic staining, using Shorr's differential staining method,<sup>16</sup> cannot always be relied upon, in our experience. Although highly cornified

a more favorable interpretation. On the supposition that the specific reaction of the vaginal mucosa to the onset of progesterone activity is folding and aggregation, associated with inhibition of estrogen cornification, one should expect a curve of ovarian function similar to that illustrated in Fig. 5. It will be seen that the degree of cornification rises steadily to a high peak and then sharply declines. Associated with this abrupt drop in cornification, a sharp rise in desquamation index from zero or near zero levels is simultaneously seen. This point represents ovulation as diagnosed by the vaginal smear technique. The absence of ovulation, by this method, may be illustrated by Fig. 6. It is apparent that the practically straight lines obtained for desquamation and cornification indicate that progesterone in amounts sufficient to affect the vagina has not been liberated. In our series, however, it has been possible to secure very few cases which show the type of curve illustrated in Fig. 5. More representative of typical cycles encountered are those illustrated in Figs. 7 and 8. Here distinct evidence of desquamation may be present at any stage of the cycle, bordering at levels, indistinguishable from progesterone effects. It is apparent, however, that, when the inhibition of the cornification index is considered simultaneously, it is possible to distinguish between a true and a false progesterone response. Thus, in Fig. 7, the desquamation peak at Day 5 is clearly not ovulation, since the cornification index did not simultaneously fall with the rise in desquamation nor does the desquamation index remain high.

These artifact peaks of desquamation appear in a large percentage of the cycles studied, but need not be considered as serious objections to the smear method, since by comparing the desquamation index with the cornification index a check is furnished for the evaluation of progesterone activity. However, it is obvious that the analysis of a single or an incomplete group of vaginal smears to determine whether or not the patient has ovulated is impossible. No final explanation at the moment can be advanced for the artifact desquamations. Coitus is not the causative factor, since in numerous instances where coitus had taken place the night before, desquamation in the vaginal smear was not evident. Furthermore, the desquamation artifacts do not appear to be related to any single method of taking the smears.

Another confusing point was encountered in studying the vaginal smears of several patients. Rubenstein<sup>20</sup> has observed in a patient with a persistently high estrogen level, produced by implantation of estrogenic pellets, that the vaginal smear picture may change abruptly from a high degree of cornification without desquamation to one wherein significant desquamation appears, without the occurrence of ovulation. He believes that cornification is primarily a degenerative process produced by estrogen and, even in the absence of progesterone, may even-

cells usually stain red, and less cornified cells stain green, it has been possible to demonstrate green-staining cells with highly pyknotic nuclei, and red-staining cells with large vesicular nuclei. Urinary pregnanediol glucuronide (P. G.) was determined by the modified method of Venning.<sup>19</sup> The figures are uncorrected for reasons that will be made clear in the body of this paper. The urines were collected over twenty-four-hour periods. In order to prevent hydrolysis of the pregnanediol complex during collection and before laboratory work-up, the following procedure was adopted: the patients were instructed to collect urines in bottles containing 200 c.c. of butyl alcohol; to shake the collection bottle after each addition of each sample; to keep the urine bottle refrigerated;

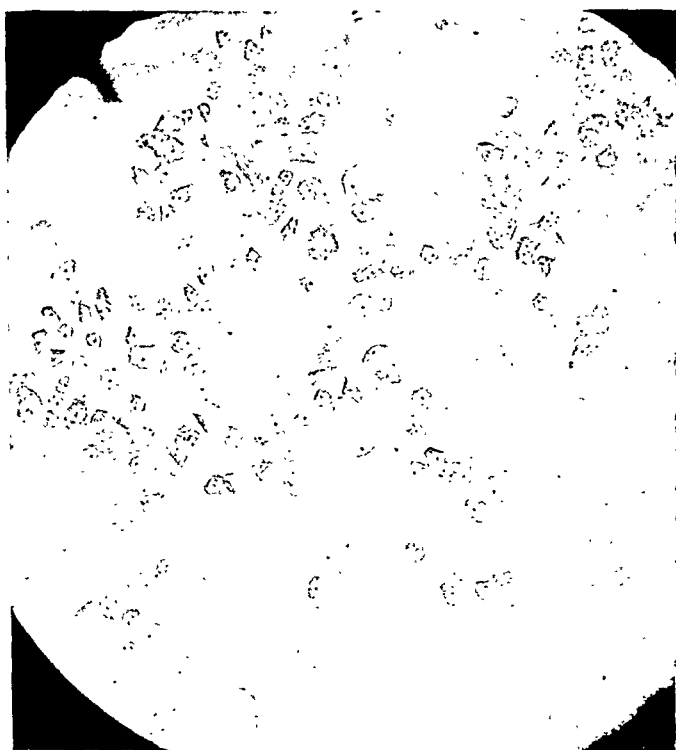


Fig. 4.—A low-power photomicrograph ( $\times 100$ ) of Fig. 2, illustrating absence of cell aggregation in a preovulatory vaginal smear.

and finally to bring the urine to the laboratory immediately after the collection period. This procedure was adopted on the premise that extraction of the pregnanediol complex by the butyl alcohol already in the bottle would inhibit bacterial or enzymatic hydrolysis of the complex. Unpublished experiments indicate that pregnanediol glucuronide is relatively stable under these conditions.

#### DISCUSSION OF RESULTS

First attempts to analyze and correlate our vaginal smear and urinary pregnanediol studies were met with considerable difficulty and confusion which almost precipitated a condemnation of the value of both methods. However, continued efforts clarified our results and justified



sequence, in that each period of desquamation is transient. Furthermore, there exists a persistently high degree of cornification, broken in most instances only when accompanied by the rise of the desquamatory reaction. The vaginal smear pictures of several other cases of hyperestronism under our observation demonstrated the same qualitative cyclic changes seen in Fig. 9.

Although the occurrence of more than one ovulation per cycle has been suggested by some investigators, the presumed occurrence of three or four ovulations in one cycle seems unlikely. In the case illustrated by Fig. 9, urinary pregnanediol glucuronide was absent and a proliferative endometrium was found at a time when one of the desquamation peaks occurred, which further precludes the possibility of the occurrence of ovulation.

It has been clearly recognized that the excretion of pregnanediol glucuronide in the nonpregnant woman depends, not only upon the secretion of progesterone by the ovary, but also upon endometrial, hepatic, and renal factors.<sup>21</sup> That progesterone need not necessarily be metabolized through the pregnanediol-P.G. route has been adequately demonstrated in primates and in common laboratory animals.<sup>22, 23</sup> Presumably this alternative pathway of progesterone metabolism is operative in human beings as well, since the recovery of parenterally administered progesterone as urinary pregnanediol glucuronide may vary from 0 to 70 per cent.<sup>24</sup> In this laboratory, we have confirmed the finding that progesterone is not quantitatively converted to pregnanediol glucuronide in women. With the participation of extraovarian factors in the metabolism of progesterone established, it is clear that quantitative evaluation of luteal activity is not obtainable by pregnanediol glucuronide estimation in the absence of quantitative information regarding the efficiency of all factors which take part in the excretion of pregnanediol glucuronide. Furthermore, the presence or absence of urinary pregnanediol glucuronide may not serve as a qualitative test for luteal activity, since it is possible to obtain zero values for pregnanediol glucuronide in the presence of circulating progesterone. Recognizing these difficulties, it is still possible to utilize pregnanediol glucuronide determination for useful information regarding luteal activity. The presence of urinary pregnanediol glucuronide may be taken as strong suggestive evidence for functional luteal tissue and the quantity of pregnanediol glucuronide excreted represents a minimal estimate of the amount of metabolized progesterone. Using this reasoning as our basis for interpreting the significance of pregnanediol glucuronide determinations we have correlated vaginal smears with urinary excretions of pregnanediol glucuronide. One should expect that the presence of luteal activity diagnosed by the smear technique should in most cases be accompanied by a simultaneous excretion of pregnanediol glucuronide. If a vaginal smear indicates luteal activity,

tually terminate in a desquamation. He concludes that this desquamation is just an advanced step in the degenerative process, which does not occur under normal conditions with a normal estrogen level. Fig. 9 is a chart of the vaginal smears taken from a patient who is a sterility

Fig. 5.

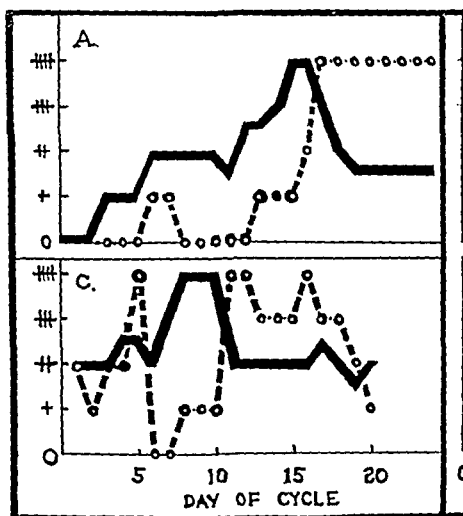


Fig. 6.

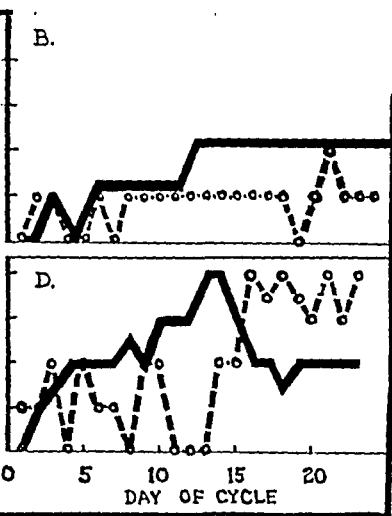


Fig. 7.

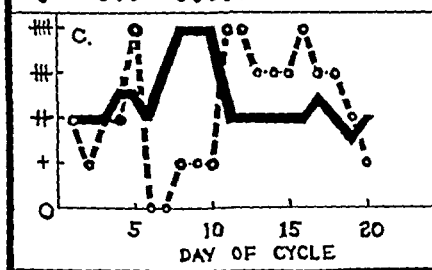


Fig. 8.

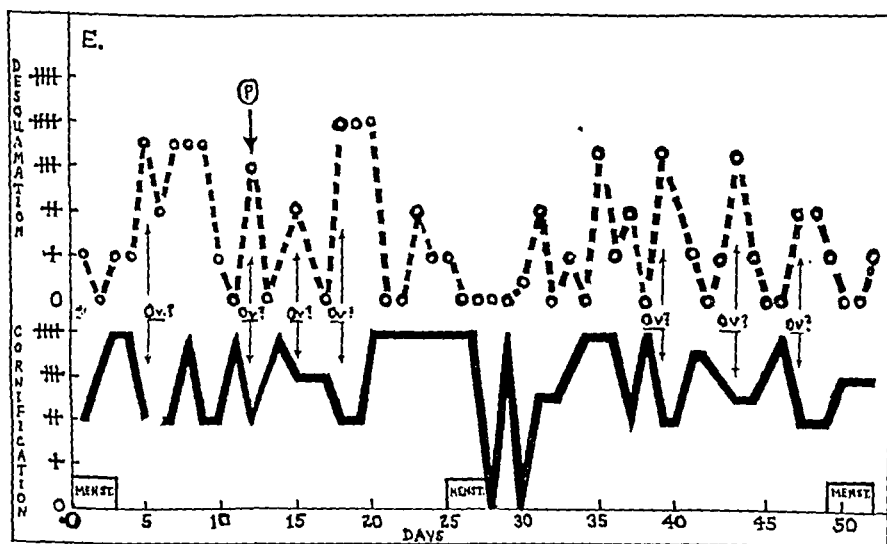
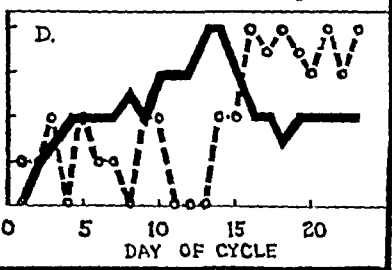


Fig. 9.

Figs. 5, 6, 7, 8, and 9.—Illustrating graphically the daily cornification and desquamation changes in 5 different patients. Cornification is represented by the solid line ———, while desquamation is shown by the broken line - - - - -.

problem of many years and is an excellent illustration of this observation made by Rubenstein. It will be seen that in the two cycles illustrated, numerous peaks of desquamation occur which might be diagnosed as the result of ovulation. The curve, however, departs from the usual

purity present in the urine of the patient, and the vaginal smear interpretation was correct.

Table II illustrates data on Case J. M., part of whose smear history appears in Fig. 9. In the section on vaginal smears reasons were advanced as proof that the smear pattern indicated no luteal activity. Here again, definite amounts of this pregnanediol glucuronide-like material were present in the urine, which by chemical analysis proved not to be pregnanediol glucuronide, and therefore confirms our analysis of the smear. These data clearly indicate the necessity for the independent determination of the purity of small amounts of pregnanediol glucuronide by means other than solubility properties. This may be accomplished by the method developed in this laboratory or by the method recently reported by Allen and Viergiver.<sup>26</sup>

TABLE II. COMPARISON BETWEEN GRAVIMETRIC AND CHEMICAL REDUCTION METHODS FOR ESTIMATION OF PREGNANEDIOL GLUCURONIDATE (CASE J. M.)

| DATE     | DAY OF CYCLE<br>(ONSET OF MENST. = 1) | PREGNANEDIOL GLUCURONIDATE<br>MG./24 HR. |          |            | VAGINAL SMEAR |       |
|----------|---------------------------------------|--|----------|------------|---------------|-------|
|          |                                       | GRAV.                                    | CHEM.    | % IMPURITY | CORN.         | DESQ. |
| 10/11/41 | 5                                     | 2.4                                      | Total    |            | 0             | +     |
| 10/12/41 | 6                                     | 2.7                                      | 13.9 mg. |            | ++            | +++   |
| 10/13/41 | 7                                     | 2.2                                      | tested   | 96         | +++           | 0     |
| 10/14/41 | 8                                     | 2.0                                      | = 0.5    |            | +++           | +     |
| 10/15/41 | 9                                     | 2.5                                      | mg.      |            | ++++          | 0     |
| 10/16/41 | 10                                    | 0.5                                      |          |            | ++++          | +++   |
| 10/17/41 | 11                                    | 0.8                                      |          |            | ++++          | +     |
| 10/18/41 | 12                                    | 0.8                                      |          |            | ++            | +++   |
| 10/19/41 | 13                                    | 0.4                                      | -        | -          | ++++          | 0     |
| 10/20/41 | 14                                    | 0.3                                      | -        | -          | ++            | +++   |
| 10/21/41 | 15                                    | 1.3                                      | -        | -          | ++            | +     |
| 10/22/41 | 16                                    | 6.7                                      | 0        | 100        | +++           | +     |
| 10/23/41 | 17                                    | 1.5                                      | 0        | 100        | ++++          | 0     |
| 10/24/41 | 18                                    | 1.5                                      | 0        | 100        | +++           | +     |
| 10/25/41 | 19                                    | 1.5                                      | 0        | 100        | ++            | ++    |
| 10/26/41 | 20                                    | 0.2                                      | -        | -          | ++            | ++    |
| 10/27/41 | 21                                    | 6.0                                      | 0.9      | 85         | +++           | 0     |

#### CONCLUSIONS

1. The evaluation of ovarian function by the vaginal smear method is complicated by numerous factors.

2. In most cases these factors may be properly interpreted by taking daily vaginal smears throughout an entire cycle.

3. Artifact peaks of desquamation frequently occur without a corresponding abrupt drop in cornification and do not signify ovulation.

4. Persistently high levels of estrogen may induce a desquamation similar to that produced by progesterone during the luteal phase of the cycle.

5. The supposition that the modifications reported by Venning for pregnanediol glucuronide determination eliminates most of the impurities in the final product can no longer be considered tenable.

6. A new method for the quantitative determination of pregnanediol glucuronide based upon the copper reducing activity of the glucuronic

the absence of pregnanediol glucuronidate in urine collected at the same time, does not necessarily indict the vaginal smear technique, since the result might be conceivably explained as a consequence of an altered metabolism of progesterone. The vaginal smear technique, however, should be positive for luteal activity when the urine shows pregnanediol glucuronidate (neglecting adrenocortical tumors and the like).

Table I illustrates our results on Case S. R. Here it will be seen that definite amounts of a material of solubility properties similar to pregnanediol glucuronidate regularly appeared in the urine, although no evidence of luteal activity was found in the vaginal smears. Attempts to obtain melting point determinations on this material failed, although it may be emphasized here that this pregnanediol glucuronidate-like material could be obtained after three precipitations from water with

TABLE I. COMPARISON BETWEEN GRAVIMETRIC AND CHEMICAL REDUCTION METHOD FOR ESTIMATION OF PREGNANEDIOL GLUCURONIDATE (CASE S. P.)

| DATE     | DAY OF CYCLE<br>(ONSET OF MENST.<br>= 1) | PREGNANEDIOL GLUCURONIDATE<br>MG./24 HR. |       |            | VAGINAL SMEAR |       |
|----------|--|--|-------|------------|---------------|-------|
|          |  | GRAV.                                    | CHEM. | % IMPURITY | CORN.         | DESQ. |
| 8/17/41  | 17                                       | 0  | —     | —          | +             | +     |
| 8/18/41  | 18                                       | —  | —     | —          | +             | +     |
| 8/19/41  | 19                                       | 1.8                                      | —     | —          | +             | +     |
| 8/20/41  | 20                                       | 5.2                                      | —     | —          | +             | ++    |
| 8/21/41  | 21                                       | 2.0                                      | —     | —          | +             | +     |
| 8/22/41  | 22                                       | 1.6                                      | —     | —          | ++            | ++    |
| 8/23/41  | 23                                       | 4.8                                      | —     | —          | +             | +     |
| 8/24/41  | 24                                       | 2.8                                      | —     | —          | ++            | +     |
| 8/25/41  | 25                                       | 3.2                                      | —     | —          | +             | +     |
| 11/ 6/41 | 17                                       | 1.6                                      | 0     | 100        | +             | 0     |
| 11/ 7/41 | 18                                       | 3.0                                      | 0.2   | 93         | +             | 0     |
| 11/ 8/41 | 19                                       | 3.6                                      | 0     | 100        | ++            | +     |
| 11/ 9/41 | 20                                       | —  | —     | —          | ++            | ++    |
| 11/10/41 | 21                                       | 1.6                                      | 0     | 100        | ++            | +     |
| 11/11/41 | 22                                       | 2.0                                      | 0     | 100        | ++            | +     |
| 11/12/41 | 23                                       | —  | —     | —          | —             | —     |
| 11/13/41 | 24                                       | 4.0                                      | 0     | 100        | ++            | 0     |

acetone and on macroscopic examination appeared indistinguishable from small amounts of pure amorphous pregnanediol glucuronidate. To check quantitatively the purity of this material isolated by the method of Venning,<sup>19</sup> a chemical method was devised in this laboratory wherein pregnanediol glucuronidate is determined by the estimation of copper reducing activity obtained after acid hydrolysis of the pregnanediol glucuronidate sample.<sup>25</sup>

With the development of a method to check the purity of pregnanediol glucuronidate isolated from urine, simultaneous smears and pregnanediol glucuronidate determinations on patient S. R. were repeated two months later. These data are also illustrated in Table I. It will be seen once again that definite amounts of a pregnanediol glucuronidate-like material were obtained regularly in the absence of luteal activity as diagnosed by vaginal smear. However, this material regularly failed to give the chemical test for pregnanediol glucuronidate. It, therefore, appears that this material was not pregnanediol glucuronidate, but some im-

human being with confirmation at laparotomy. In this instance a recently ruptured follicle was observed and a portion of the ovary containing it was removed and studied microscopically. Rock, Reboul and Wiggers<sup>8</sup> extended these findings to a larger group and confirmed the experiment, although there were some discrepancies.

The consequences of this new approach are sufficiently important to require rigorous validation of the procedure, under a wide variety of conditions, especially since Rock<sup>9</sup> has recently reversed his original stand. Boling and others<sup>2</sup> have applied the technique to a very complete study of the entire estrous cycle in the albino rat and have shown, among other things, a clear-cut and significant alteration in the electrical pattern from the inception of heat to its termination. Moreover, Langman and Burr<sup>6</sup> reported characteristic electrical changes in uterine activity throughout the menstrual cycle in women. In continuation of these studies, an improved and somewhat simplified technique has been developed which makes it possible to record the changes in voltage gradient which exist between the human cervix uteri and some indifferent point on the surface of the body, such as the ankle.

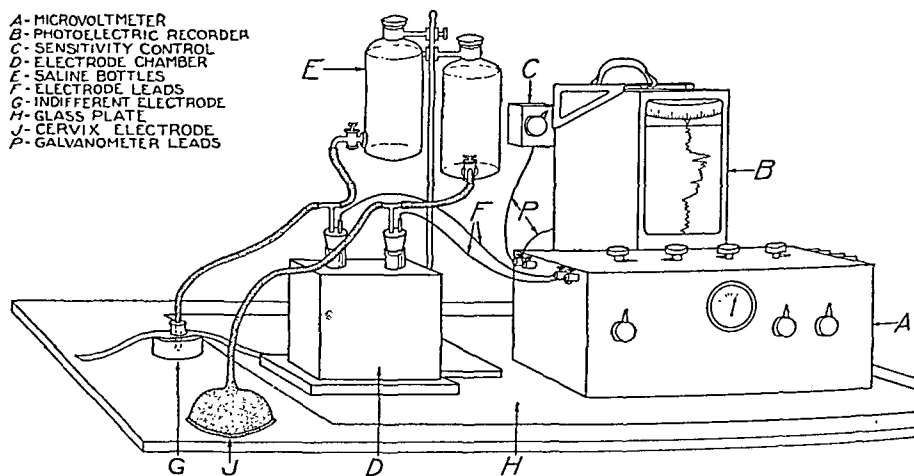


Fig. 1.—Diagrammatic sketch of apparatus.

#### PRESENT TECHNIQUE

The apparatus used in the procedure was a Burr-Lane-Nims DC microvoltmeter with a General Electric photoelectric recorder as a recording galvanometer (Fig. 1). The paper speed was one inch in five minutes and its sensitivity one millivolt per division. The zero baseline was in the center of the chart. Deflections of the pen to the right indicated positive polarity of the input lead to the grid of the microvoltmeter; deflections to the left, negative polarity of this lead. Contact of the microvoltmeter with the patient was made by a pair of nonpolarizable reversible silver-silver chloride electrodes immersed in physiologic salt solution. From the chambers containing these electrodes, rubber tubes were led to the patient. The one from the ground electrode terminated in a sponge rubber disc which could be strapped to the ankle. This

acid obtained after acid hydrolysis is referred to and offered as a means of eliminating the source of error experienced with the method of Venning.<sup>25</sup>

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# ELECTROMETRIC TIMING OF HUMAN OVULATION\*

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INVESTIGATORS have long sought an adequate method for determining with certainty the time of ovulation in animals and in man. The usual methods of mating at selected times and the examination of the generative tract at laparotomy have given us a good deal of valuable information. In man these procedures have been time-consuming and not altogether satisfactory, hence the report by Burr, Hill and Allen<sup>4</sup> that ovulation in the rabbit was accompanied by significant modifications of an electrical pattern in the intact animal, offered a new procedure fraught with many possibilities. The findings were confirmed by Reboul, Friedgood and Davis<sup>7</sup> and extended by Altman.<sup>1</sup> Subsequently Burr, Musselman, Barton and Kelley<sup>5</sup> reported an electrometric change in the

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In Patients 1, 2, and 3, the first ones studied, various techniques for the timing of ovulation were employed, in addition to the electrometric procedure. Five artificial inseminations were carried out at the time when ovulation was believed to have occurred. It should be noted that in these patients the assumed time of ovulation did not correspond exactly to the day of the negative shift of the cervix. In Records 1 and 5, however, the correspondence was close. Nevertheless, in none of these patients did pregnancy supervene. There are several explanations for the failures other than the absence of exact correspondence of insemination and negative shift, for the previous matings in these patients had all been sterile.

In Patient 4, the negative shift of the cervix occurred on the thirteenth and on the fourteenth day and was accompanied by intermenstrual pain. There is some evidence in the literature which suggests that intermenstrual pain may be associated with follicular rupture. The second

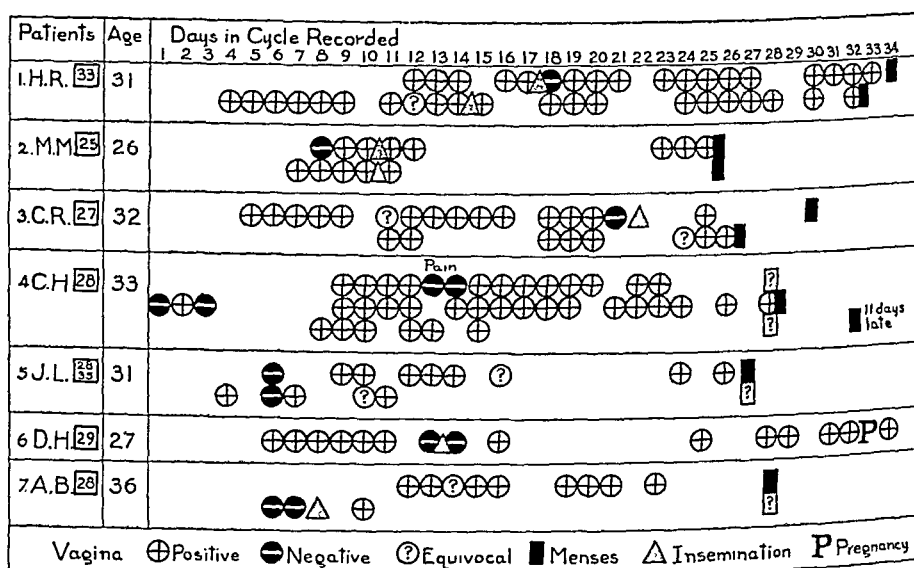


Fig. 2.—A chart of the events on successive days of the menstrual cycle.

cycle recorded in this patient showed an anomaly which is hard to explain. The cervix was negative on the first and third days of menses and no other negative records were obtained for the rest of that cycle. If the negativity of the cervix occurs at the time of ovulation and at no other time in the cycle, then this record would strengthen the view that ovulation may occur at any time in the cycle, even during menstruation.

Patient 6 deserves special attention. On the thirteenth day of the cycle, the cervix was recorded as 8 mv. negative, and on the fourteenth day this was increased to 16 mv. negative. At the end of the recording, the patient was artificially inseminated with donor sperm. As is indicated on the chart, the patient was studied occasionally from then until the twenty-ninth day of the cycle, or fifteen days after the insemination. On that day there appeared on the record a series of repeated rather abrupt decreases in the potential difference. The magnitude was 4 mv. and the frequency 8 mv. for each five-minute period (Fig. 3, C). These were surprisingly regular and appeared throughout the period of record-

constituted the reference or cold electrode and its exact location on the surface of the body did not seem to be important. The ankle was chosen for convenience. The other electrode chamber was connected to the patient by means of a rubber tube, the outer end of which was cemented into the dome of a thin rubber cervical diaphragm. The cavity of the diaphragm was packed with cotton saturated with normal salt solution and was readily placed over the cervix. Both tubes were filled with saline, taking care to see that there were no bubbles of air in the lumen of the tubes or between the tubes and the surfaces of the body. In practice, the patient lay comfortably on an examining table for periods varying in time from fifteen minutes to more than an hour. No discomfort or pain was encountered at any time. It should be noted that this technique made it possible to record electrical changes in the intact organism. Hence, at all times, there was a minimal disturbance in normal physiologic processes. The use of silver-silver chloride electrodes gave assurance of a faithful record of true changes of potential difference without the artifacts of contact potential, such as are encountered when metal is brought directly into contact with body surfaces. In practice, these electrodes are stable and introduce no artificial e.m.f.'s in to the external circuit. While the microvoltmeter responds adequately to voltage changes at wide differences in frequencies, the recording galvanometer used imposes certain limitations on the records. The period of the galvanometer used is approximately three seconds. As a result, it did not respond readily to relatively rapid changes, such as accompany the heart, nerves, or striated muscle. Fortunately, however, nonstriated muscle contractions produce electrical changes of much lower frequency. Faithful records, therefore, could be obtained.

The cases were selected from the patients of a gynecologic practice and the studies were carried out in the office. The procedure was employed as a means of improving on the techniques previously used (Langman and Burr<sup>6</sup>) in an electrical study of uterine mobility during the menstrual cycle. While interesting data on this point were obtained, it was overshadowed by an unexpected finding, which it is the purpose of this report to present.

#### ANALYSES AND DISCUSSIONS

Approximately 150 records have been taken from 7 women on the majority of the days of the menstrual cycle. The studies showed that most commonly throughout the menstrual cycle the cervix was positive to the ankle from 5 to 25 mv. In 9 of the 14 cycles studied, the cervix became negative, an equivalent amount on at least one day of each cycle. In four of these, the cervix remained negative for two days. The days of the cycle on which the negativity appeared were the third, sixth, seventh, eighth, thirteenth, fourteenth, eighteenth, or twenty-first. In five cycles either no negative shift occurred or it was equivocal. The general distribution of these results is shown in Fig. 2. It will be noted that there are many gaps in each cycle, due to the necessary exigencies of an office practice. In a number of instances the recorded potential difference was so near the baseline that it was called equivocal and is marked on the chart with a question mark.



to as much as 30 or 35 mv. and usually remained there until the actual onset of bleeding. With the onset of the flow, the voltage difference dropped to more nearly the normal 15 mv.

The history of Patient 7 (A. B.) is also of considerable interest. Although apparently a healthy young woman, with a regular twenty-eight-day cycle, and married for several years, mating had been infertile. On examination it was found that the uterus was considerably smaller than usual, approaching the infantile type. However, a number of records were taken as is shown in Fig. 2, and a negative shift appeared on the sixth and seventh days of the second cycle. Immediately following this, artificial insemination, using husband's sperm, was carried out. Twenty-one days later, when menses would have normally appeared, none occurred. However, menses did appear eleven days later. On the day before the onset of menses, the patient, as an air raid warden, had found it necessary to run up and down stairs frequently. It is not impossible, therefore, that fertilization might have occurred but with subsequent early abortion.

In an attempt to build up the uterine mechanism in the subsequent cycle, estradiol benzoate (10,000 R.U.) was administered on the eighth day. Twenty-four hours later the record shown in Fig. 3, *D* was obtained. This characteristic record is almost identical with that obtained from Patient 6 (D. H.), fifteen days after successful insemination. In both instances the records are very similar to those obtained during the period of heat in the albino rat (Boling and others<sup>3</sup>). Twenty-four hours later the same phenomenon was observed although the magnitude of the rhythmic changes was reduced and the frequency increased. On this, the tenth day, the patient was given another injection of the same amount and again on the thirteenth day. Following the last injection the rhythmical changes were present but much reduced in frequency and amplitude. Two cycles later, estradiol benzoate (4,000 R.U.) was given on the third day of the cycle. For the succeeding four or five days, there were moderate signs of uterine activity and on the ninth day a second injection of estradiol was given. Twenty-four hours later the cervix was negative and showed rhythmical changes of low magnitude but relatively high frequency. Artificial insemination with husband's sperm was carried out and frequent records taken up to the eighteenth day. At the time when subsequent menses were due, the patient gave subjective signs of pregnancy with swelling and tenderness of the breasts. An Aschheim-Zondek test, however, made a few days later, was negative and eventually menses appeared nine days late. It is possible that here again fertilization occurred with subsequent early abortion. The apparent absence of correlation between negative shift of the cervix and ovulation is important for it indicates that there is still a good deal to be learned about electrical phenomena associated with the physiology of the generative tract. Many more carefully controlled studies must be carried out before the final answer can be discovered.

#### SUMMARY AND CONCLUSIONS

The implications of the findings of this study are of considerable interest. There are obviously a good many variables involved in the physiology of the generative tract. This is also true of the single event of ovulation. The fact that it was possible to get at least one positive correlation makes it worthwhile to extend these studies to as many pa-

ing. Two days later the records showed the same kind of phenomena but by the thirty-second day they disappeared. At this time the breasts became tender and the patient gave subjective evidence of pregnancy. This was confirmed by the Aschheim-Zondek test and by subsequent history (Fig. 3, A, B, C).

The situation in this particular patient was important because, although the patient had been married for several years, mating had been infertile. On examination this was shown to be due to azoospermia. Artificial insemination with donor sperm was resorted to on this one occasion only, in order to produce the desired pregnancy. The circumstances, therefore, acted as a very adequate control for the experiment. The fact that artificial insemination was successful suggests that the negative shift occurred at the time of ovulation, as it does in the albino rat.

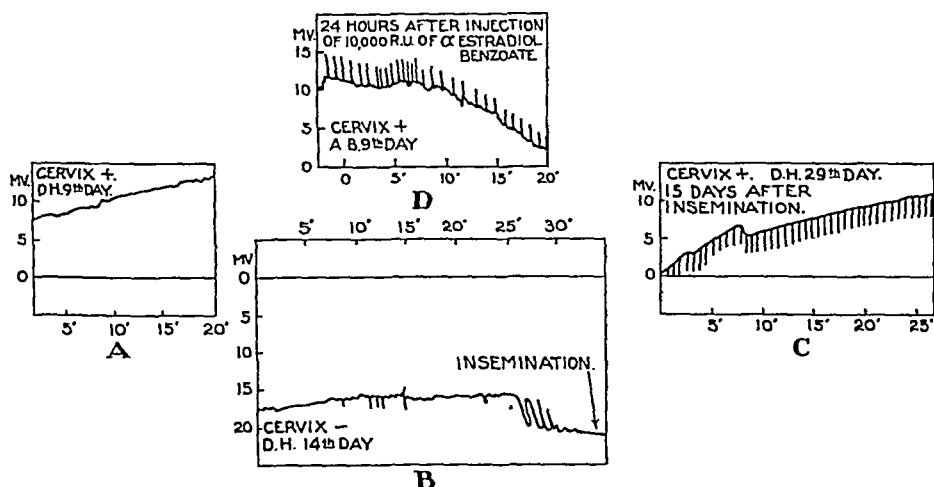


Fig. 3.—Tracings of photoelectric recordings. A, The ninth day of D. H. showing cervix positive. B, Fourteenth day of same patient showing cervix negative. C, Fifteenth day after insemination showing electrical activity of the cervix. D, Ninth day of A. B. showing electrical activity of the cervix following hormone injection.

It is noteworthy that the regular and rhythmic changes in electrical potentials described above appeared on the day when the normal menses would have occurred. The character of these changes is interesting, because they are very similar to the kind of phenomena which have been recorded in the generative tract of the albino rat during estrus. Boling has shown that these rhythmic phenomena can be induced in spayed animals by the administration of hormones. Moreover, it is generally believed that some two weeks after fertilization there is a sharp rise in the hormone level in the circulating body fluids. The evidence here presented indicates the probability that the impact of chemical agents on the generative tract produced significant changes in the electrical pattern.

Since the general muscular activity of the uterus, as reflected in changing potentials, is an important element in the physiology of the generative tract, it should be noted that all the electrical records showed a higher level of activity as early as the sixth and as late as the twenty-first day of the cycle. This fits in very well with previous findings. An additional interesting observation was that on the fourth or fifth days prior to the onset of a succeeding menses, the positivity of the cervix increased

tive. The patient was artificially inseminated on this day with husband's sperm. She was studied subsequently, and on the nineteenth day, the cervix was only 2 mv. negative. The twentieth day showed a marked positive shift of 15 mv. potential difference, similar to the findings prior to the eighteenth day. On the thirty-first day there appeared on the record a series of repeated abrupt decreases in potential difference. These are interesting and of possible significance, because they are similar to the phenomena recorded on the twenty-ninth day of the cycle in Patient 6, previously reported, in whom pregnancy was subsequently confirmed. On the thirty-second day and daily thereafter up to, and including, the forty-first day, recordings were similar to those corresponding days in Patient 6. At this time the breasts became sensitive and tender and the patient experienced subjective evidence of pregnancy. On the forty-fifth day, fourteen days later than the usual time, patient began to bleed. It is possible that here, as in Patient 7, fertilization occurred with subsequent early abortion.

PATIENT 9.—L. B., aged 33 years, menstrual cycle thirty to thirty-two days. Infertile mating for past several years. Ten artificial inseminations, using the husband's sperm and donor sperm, had been unsuccessful. These inseminations were performed at an estimated ovulation time and at an ovulation time determined with various other techniques.

An electrometric study was begun because of the repeated failures to impregnate this patient. A negative shift was observed on the fifteenth day of the menstrual cycle in two successive cycles recorded. Artificial insemination using donor sperm was carried out on the fifteenth day of the cycle after the recording of a negative shift in potential. Following the first insemination, normal menses ensued on the thirty-second day of that cycle. When the negative shift occurred on the fifteenth day of the following month, artificial insemination with donor sperm was repeated and subsequent menses did not appear. Pregnancy was confirmed by the Aschheim-Zondek test and subsequent history. The fact that artificial insemination was successful again suggests that the negative shift occurred at the time of ovulation. The circumstances in this case can be considered as a very adequate control for the experiment.

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From a questionnaire study of 10,600 births in Manitoba in 1939 and 1940, it was concluded that only 25 per cent of the patients received adequate prenatal care. For this purpose adequate care was defined as 5 or more prenatal visits. If based on the actual investigation done by the physician during these visits, only 17 per cent received adequate care. For example, only 714 of 2,636 cases had a study of blood serology. The maternal death rate in the group with adequate care was 3.8 per 1,000 live births as compared with 4.6 in the remainder. The prenatal and neonatal mortality rates were 36.0 and 44.0 in the two groups.

CARL P. HUBER.

tients as is possible. The number of volunteer patients in an office practice is necessarily limited, so that it is desirable that the technique be employed as widely as possible. Attention, however, must be called to the fact that while the procedure is relatively simple, certain safeguards against artifacts must be employed. It should be noted that the hot lead goes to the cervix and not to the wall of the vagina. That this is important is suggested by some findings on the electrophysiology of the generative tract in the monkey where there is a very sharp gradient between the vagina and the os, with a polar reversal. Unsuspected grounds on the patient are a possible source of error. Air bubbles in the leads to the electrodes are another. Interference from other electrical devices is occasionally met with but can usually be recognized without difficulty in the photoelectrical record. The procedure is simple enough, however, so that the studies are being currently continued.

A second aspect of the findings is the pronounced effect of the injection of a hormone upon the electrical record. This corroborates in the human experimental data derived from the albino rat. They suggest the possibility of studying the effect of a variety of hormones upon generative physiology. The technique has the advantage of being employed on the intact organism, interfering little with the normal physiology. It is not impossible, therefore, that it can be utilized as an effective adjunct to other procedures in the study of endocrine physiology. This report is presented not as a final exposition but in the hope that it will stimulate others to extend these studies.

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#### ADDENDUM

We wish to report observations completed on two additional women since submitting the original manuscript for publication. They substantiate our previous findings and in the case of Patient L. B., add one more positive correlation with ovulation time to our series.

PATIENT 8.—M. J., aged 34 years, had a history of sterility for two and one-half years; menstrual cycle for the past year had been regular, thirty-one to thirty-two days. On the eighteenth day of the cycle the cervix was recorded as 5 to 15 mv. negative, having previously been posi-

stigmas of endocrine origin were carefully noted. In all cases where examination left doubt as to gravidity, the Friedman modification of the Aschheim-Zondek test was done routinely.

In order to determine the efficacy of this drug as a diagnostic test for pregnancy, only those patients who asked for such a diagnosis are included in Tables I to IV. In all, 90 such patients, complaining of temporary amenorrhea, were treated with injections of prostigmine methylsulfate. All injections were given intramuscularly, one injection per day, for periods ranging up to three days. Depending on the weight of the patient and the duration of the amenorrhea, the amount of prostigmine used was either 1 or 2 c.c. (1:2000) per injection. If the menstrual flow was precipitated before the series was completed, further injections were discontinued.

Excluding temporary vertigo and nausea which were present in about 40 per cent of all cases, no untoward effects were noted, except in one case, where after the third injection the patient collapsed. Shock lasted for about fifteen minutes, during which time there was loss of sphincter control, slowing of respiration, and almost complete disappearance of the pulse. Treatment was started and recovery was spontaneous and complete. No explanation for this peculiar reaction can be offered.

#### EXPERIMENTAL RESULTS

Originally this work was undertaken to verify the value of prostigmine as a test for possible pregnancy, based on the fact that if the patient did not bleed after a series of three injections, she was to be considered gravid. Patients are divided into three groups, according to results obtained, as correlated with either the physical findings or the Aschheim-Zondek tests:

1. Those patients diagnosed as not pregnant who bled after the injection of prostigmine.
2. Those patients who either were diagnosed as pregnant, or who subsequently proved to be pregnant who did not bleed as the result of the action of prostigmine.
3. All other patients, in whom results with prostigmine failed to agree with other observations.

As has been mentioned previously, the following series is limited to only those cases where a suspicion of pregnancy on the part of the patient existed. No attempt to induce menstruation was made where the amenorrhea was due to glandular involvement or where no indication for the precipitation of the flow existed. Table I represents in brief, the histories of 57 cases, proved nonpregnant either by physical examination, by the Aschheim-Zondek test, or by further observation in which the action of prostigmine was sufficient to bring about the delayed vaginal bleeding.

# PROSTIGMINE METHYLSULFATE AND DELAYED MENSTRUATION

## EVALUATION OF PROSTIGMINE AS A TEST FOR PREGNANCY

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RECENT studies (Hechter, Lev, and Soskin;<sup>1</sup> Soskin, Wachtel, and Hechter<sup>2</sup>) have suggested that prostigmine methylsulfate might precipitate a blood flow in women whose periods were delayed by causes other than endocrine dysfunction or early pregnancy. These workers<sup>2</sup> have further attempted to demonstrate that this action is so specific that it could be used as a diagnostic measure in differentiating a "physiologic delay" from early pregnancy, "with the same degree of accuracy as is possible with the Aschheim-Zondek test." Weisman,<sup>3</sup> however, criticized the rationale of the procedure as a differential diagnosis since so many qualifying conditions (puberty, menopause, systemic disorders, endocrinopathies, etc.) were introduced. Winter,<sup>4</sup> furthermore, clinically demonstrated failures of this procedure in inducing menstruation when gravidity was not present. Greenhill<sup>5</sup> agrees essentially with these authorities.

Soskin and others suggest that prostigmine be administered in daily doses of from 1 to 2 c.c. (1:2,000) for three consecutive days. If bleeding is induced, the patient is considered to be nonpregnant. They state that clinical evidence is available to demonstrate that prostigmine is nonabortive, nonecbolic, will not induce premature labor, and has no effect on the uterine musculature even at full term (Schofer<sup>6</sup> and Spoto<sup>7</sup>).

Since the original publication,<sup>2</sup> much clinical material has become available for study of the menstrual phenomena induced with prostigmine. It is the purpose of this investigation first to assay the efficacy of this drug as a diagnostic measure for determining early pregnancy; and second, to disclose as far as possible the actual modus operandi of the drug in producing menstrual bleeding.

### GENERAL METHODS

A complete history, including a menstrual history, was taken on all patients. Physical examination, with special attention being given to a complete pelvic examination, was done routinely. Furthermore, all

TABLE III. FAILURE OF PROSTIGMINE TO DIAGNOSE PREGNANCY

| NO. | NAME  | AGE | GRAVIDITY | CATAMENIA  | DELAY                 | STATUS  | INJECTION      | RESULTS   |
|-----|-------|-----|-----------|--|-----------------------|---|----------------|---|
| 43  | E. S. | 46  | 0         | 15/28/4; periods decreasing in amount during last year; few menopausal symptoms (subjective) present | 30 days               | Physical examination negative; Aschheim-Zondek negative           | 4 x 3          | None  |
| 44  | D. G. | 48  | iv        | 10/27-29/6; no subjective symptoms; interval increased by 2 weeks during last year                   | 30 days               | Slight enlargement of uterus; Aschheim-Zondek negative            | 4 x 2          | None; spotted for 1 day about 2 months after injection  |
| 45  | N. S. | 42  | ii        | 11/28/3-5; no irregularity of menses; some menopausal symptoms (?)                                   | Approximately 1 month | Small soft uterus + Chadwick's sign; Aschheim-Zondek negative     | 3 x 2<br>1 x 3 | No results in 1 week; no further follow-up  |
| 46  | F. L. | 20  | 0         | 17/25-27/3; periods irregular; married 3 months  | Approximately 5 weeks | Soft uterus; not enlarged; Aschheim-Zondek negative               | 3 x 2          | No result; bled spontaneously 3½ weeks after last injection   |
| 64  | A. S. | 26  | 0         | 16/6 weeks/3; no irregularity of periods; no endocrine stigmas                                       | 4 weeks               | Physical negative; Aschheim-Zondek negative                       | 3 x 1          | No result in 10 days  |
| 49  | D. J. | 22  | 0         | 14/30-35/7   | ? 2 weeks             | Patient felt pregnant; Aschheim-Zondek doubtfully positive        | 3 x 2          | Stained after second injection; bled profusely after third, with cramps and clots                         |
| 65  | R. B. | 26  | 0         | 15/26/3; no irregularities of periods  | 9 days                | Pregnant to examination. No Aschheim-Zondek done                  | 3 x 1          | Bled; examined 1 month later and was 10 weeks gravid  |
| 82  | F. T. | 29  | i         | 13/29-31/5; no irregularity of periods, 6 months post-partum   | 15 days               | Not pregnant to examination, Aschheim-Zondek negative; very obese | 3 x 2          | No bleeding in 5 days   |
| 83  | E. B. | 44  | iv        | 12/28/5; decreased flow for 6 months   | Approximately 3 weeks | Not pregnant to examination; no atrophy of genitals               | 3 x 1          | Bled 1 week after last injection (skipped one entire cycle)   |
| 47  | E. M. | 31  | iii       | 14/25-31/5; severe dysmenorrhea  | 11 days               | Pregnant to examination ? of cystic ovary on right                | 3 x 1          | Bled for 2 days following last injection; bled 1 month later for 3 days; diagnosed as continued pregnancy |
| 69  | S. C. | 26  | ii        | 12½/21-28/5; dysmenorrhea; oligomenorrhea  | 18 days               | Uterus small; tender in right adnexa; Aschheim-Zondek positive    | 2 x 1          | Spotted 17 hours after second injection; ? of ectopic. Operated for "emergency," 5 days later             |
| 67  | W. M. | 29  | 0         | 12/28/3; mild dysmenorrhea   | 14 days               | Aschheim-Zondek negative  | 2 x 1<br>1 x 2 | No bleeding after third injection. Bled spontaneously and normally 56 days after the last menses          |

In reviewing Table I, one to three injections (average 2.4) of from 1 to 2 c.c. of a 1:2000 solution of prostigmine methylsulfate were given to 57 women whose ages varied from 18 to 44 years, resulting in starting delayed menstrual flow. Bleeding occurred in from one to seventy-two hours after the last injection had been administered, and the average lapse of time was fourteen hours. This interval was not related in any

TABLE I. SUCCESS OF PROSTIGMINE IN INDUCTION OF DELAYED MENSTRUATION (NONPREGNANT)

| GROUP | NO. CASES | DELAY*      | AVERAGE DELAY | AVERAGE NUMBER OF INJECTIONS† | RESPONSE  |
|-------|-----------|-------------|---------------|-------------------------------|---|
| I     | 5         | 3-7 da.     | 5.5 da.       | 2-3                           | 1 to 24 hours (average 12.5 hours) after last injection |
| II    | 25        | 8-14 da.    | 11.4 da.      | 2-3                           | 3 to 36 hours (average 11.4 hours) after last injection |
| III   | 22        | 2-4 wk.     | 24 da.        | 2-4                           | 1 to 72 hours (average 11.1 hours) after last injection |
| IV    | 5         | Over 4 wk.  | 6.2 wk.       | 2-3                           | 1 to 24 hours (average 15.5 hours) after last injection |
| Total | 57        | 3 da.-8 wk. | 17.7 da.      | 2-4                           | 1 to 72 hours (average 14 hours)                        |

\*Absence of pregnancy determined by: Aschheim-Zondek test, 28; physical examination and follow-up, 29.

†Injections: 1 c.c. of 1:2000 solution of prostigmine methylsulfate.

way either to the amount, or the number of injections, nor was it associated with the duration of amenorrhea preceding injection therapy. This delay varied in this series from three days to two months, the average being 17.7 days. All patients were diagnosed as nonpregnant either by physical examination or by the Aschheim-Zondek test.

Obversely, in contrast with the resultant bleeding following prostigmine in the nonpregnant, was the lack of flow in cases in which a definite gravidity was present. Diagnosis of pregnancy was made as often as possible by physical examination, and was checked in most instances by the Friedman test. Follow-ups to corroborate the diagnosis

TABLE II. FAILURE OF PROSTIGMINE IN INDUCTION OF DELAYED MENSTRUATION IN PREGNANCY

| GROUP | NO. CASES | DELAY*       | AVERAGE DELAY | AVERAGE NUMBER OF INJECTIONS† | REMARKS  |
|-------|-----------|--------------|---------------|-------------------------------|--|
| I     | 4         | 4-7 da.      | 6 da.         | 3+                            | No bleeding  |
| II    | 6         | 8-14 da.     | 11.8 da.      | 3+                            | No bleeding  |
| III   | 8         | 14-28 da.    | 21.2 da.      | 3+                            | One patient spotted after third injection; no other bleeding |
| IV    | 3         | 6-12 wk.     | 8.6 wk.       | 3+                            | No bleeding  |
| Total | 21        | 4 da.-12 wk. | 21.6 da.      | 3+                            |  |

\*Pregnancy diagnosed by: Aschheim-Zondek test, 9; physical examination, 12.

†Injections: 1 c.c. of 1:2000 solution of prostigmine methylsulfate.



more accurate in all cases, regardless of the age, physical development or endocrine status of the patient, or of the presence of pelvic or systemic pathology.

It is of interest, therefore, to study in greater detail, those cases where prostigmine gave an incorrect diagnosis. This occurred in 12, or in 13 per cent, of the total number of patients tested. In 3 of these, no definite pathology could be determined which would explain the inability of prostigmine to produce bleeding, regardless of the fact that no pregnancy was present (Cases 46, 64, and 82). Four cases (Cases 43, 44, 45, and 83) may be classified as beginning climacteric, since some few menopausal symptoms were present. Five cases (Cases 49, 47, 69, 65, and 67) are of sufficient interest to report in more detail. Brief résumés of these case histories are as follows:

CASE 49.—Mrs. D. J., aged 22 years, who had been married one year, was first seen on Jan. 16, 1941, complaining of a menstrual delay of approximately two weeks, frequency of urination, and engorgement of the breasts. Past history was negative. Menstrual history 14/30-35/7; moderate flow, no clots, no dysmenorrhea. There had been no previous pregnancies. Her last menstrual period occurred on Dec. 2, 1940 (?). Physical examination essentially was negative. Pelvic examination revealed a slightly enlarged, softened uterus in first-degree retroversion. Hegar's sign was positive. Breasts were enlarged and heavy. Areolae were darkened slightly. The Aschheim-Zondek test on Jan. 17, 1941, showed enlarged follicles, but no hemorrhage or hemorrhagic follicles. Test was reported as "doubtful" on Jan. 19, 1941; however, it was felt that the patient was pregnant.

On January 16, 17, and 18 she received 2 c.c. of 1:2000 solution of prostigmine methylsulfate. No bleeding occurred after the first injection. There was some spotting after the second, and profuse bleeding, with clots and cramps following the third. This lasted for four days, after which there was a normal flow for three additional days.

The next menstrual period occurred on Feb. 16, 1941, and was normal.

CASE 65.—Mrs. R. B., aged 26 years, complained of menstrual delay of nine days. Catamenia 15/26-8/3; no dysmenorrhea, moderate flow. Physical examination essentially was negative. Breasts were heavy and sensitive. Pelvic examination: external genitals, normal; vagina, normal, except for positive Chadwick's sign. Cervix rather soft; uterus slightly enlarged. Diagnosis of early gravidity made. Aschheim-Zondek test not done.

On February 13, 14, and 16 she received 1 c.c. of 1:2000 solution of prostigmine. Bleeding started about five hours after the last injection was given. Patient bled similarly to a normal period for four days.

On Mar. 24, 1941, she returned to the clinic, again complaining of a delay of eight days. Prostigmine was again administered, despite the fact that a definite nine to ten weeks' gravidity was found. On March 24, 25, and 26 she received 1 c.c. of 1:2000 prostigmine without subsequent bleeding.

CASE 47.—Mrs. E. M., aged 31 years, was first seen on June 15, 1941, with a complaint of menstrual delay of eleven days. There were no

and also to determine the effect of the prostigmine on the gravidity were made frequently. Twenty-one patients who were pregnant and who were injected with prostigmine without resultant bleeding are presented in Table II.

These 21 patients (Table II) ranged in age from 17 to 40 years, averaging 26.2 years, and had experienced zero to four previous pregnancies (average 1.2). The minimal number of injections given any patient was 3, and the dosage varied from 1 to 3 c.c. of the solution. The pregnancy, as calculated from the menstrual delay, was present from four days to six weeks, with an average of 21.6 days. No bleeding resulted from these injections with the exception of slight spotting after the third injection in Case 50. It is further of interest to note that prostigmine gave a correct response in one instance before the Aschheim-Zondek test became positive (Case 103).

As has been stated, a total of 90 patients, all suspicious of being pregnant, were injected with prostigmine in an attempt to make a definite diagnosis. Of these, 78 reacted in accordance with their physical status. In contradistinction to the results presented above, are the following 12 patients (Table III) in whom incorrect menstrual reactions to the drug occurred.

Before discussing the effects noted with prostigmine, it would be desirable to summarize briefly, in table form, the results obtained in the above series. In review, therefore, 90 cases of delayed menstruation, treated as described, gave results as shown in Table IV.

TABLE IV. PERCENTAGE OF ERROR OF PROSTIGMINE AS A "DIAGNOSTIC PREGNANCY TEST"

|   |    |       |
|---|----|-------|
| Total number of cases injected                          |    | 90    |
| Patients diagnosed nonpregnant who bled                 | 57 |       |
| Patients diagnosed as pregnant who did not bleed        | 21 |       |
| Total correct results                                   | 78 |       |
| Percentage correct results                              |    | 86.6% |
| Patients not pregnant who did not bleed                 | 8  |       |
| Patients pregnant who bled (including possible ectopic) | 4  |       |
| Total errors  | 12 |       |
| Percentage error  |    | 13.4% |

#### DISCUSSION

Eighty-seven per cent of 90 consecutive nonselected cases of delayed menstruation where early pregnancy was suspected gave correct results when tested with intramuscular injections of prostigmine methylsulfate. However, if this drug is to be considered as a substitute for the standard, harmless, and technically simple Aschheim-Zondek test, it should be

were pregnant. The responses to prostigmine were checked against the findings at physical examination and, where necessary, against the Aschheim-Zondek test. Follow-up examinations to verify diagnoses were made as often as possible.

The response to the drug is fairly rapid. In the nongravid, bleeding started after an average interval of fourteen hours following the last injection. The average number of injections was 2.4. If no response was elicited after a maximum number of three injections the patient was considered to be pregnant. Translating these statistics into elapsed time, the average interval for diagnosis of pregnancy with prostigmine is at least seventy-two hours, compared with a maximum of forty-eight hours with the Aschheim-Zondek technique. Should the time element ever be an important factor for the establishment of a diagnosis, the Aschheim-Zondek test is therefore superior. However, the latter is known to err, especially on the negative side, in the early stages after the first skipped period. This is to be contrasted with the fact that all 6 patients tested during the first week of amenorrhea were accurately diagnosed as pregnant by prostigmine. This is further demonstrated by Case 103, where prostigmine produced a correct diagnosis as early as one week after the skipped period, even though at this time the Aschheim-Zondek test had not yet become positive.

Discrepancies of diagnosis were noted both in positive and negative responses. Eight patients who were not gravid continued their amenorrhea, despite the injections; 4 patients who were pregnant bled following the injections. Herein lies the greatest hazard in the use of this drug. The possibility of inducing abortion, slight as it may be, would completely obviate this test in all cases where pregnancy is extremely desired, where relative sterility is involved, and where there has been a previous history of repeated spontaneous abortions.

Moreover, other factors than those of the actual statistical studies are present, and must be analyzed and considered before the test can be evaluated. The obstetrician divides all patients into two classes: those who will not tolerate pregnancy, and those who are anxious and desirous for offspring. These latter, when delayed, even though they are not pregnant, might easily misinterpret the bleeding following the injections of prostigmine, and suspect that they have been aborted. This is especially true in pseudocyesis. Furthermore, in any case where unwanted bleeding occurs, the attending physician is placed on the defensive, and despite explanations, will almost surely lose the confidence of his patient.

On the other hand, prostigmine, as a test for pregnancy, possesses a definite psychologic advantage, from the patient's viewpoint, that the doctor "is doing something positive" both in the way of diagnosis and of therapy if the delay is physiologic. Although the physician realizes that it is not essential to bleed at clocklike intervals, it is often difficult to convince a worried female who knows only that suspended menses is indicative of pregnancy. There is no question, therefore, that the use of

subjective signs of pregnancy. Past history essentially was negative. Pelvic examination gave the impression that the uterus was slightly enlarged, and an ovarian cyst could be felt on the right ovary. Last menstrual period occurred on May 6, 1941.

On June 15, 16, and 17 she received injections of prostigmine. Following the third injection she bled for two days. On July 20 she again bled for three days and a diagnosis of a three months' pregnancy was made at that time. Diagnosis was confirmed by follow-up examinations. Patient carried through the seventh month and delivered a premature infant.

CASE 69.—Mrs. S. C., aged 26 years, gravida ii. Catamenia 12½/21-28/5. Past history negative. Menstrual history unimportant except for mild dysmenorrhea and slight oligomenorrhea. Last menstrual period occurred on August 12. She was seen on September 16 complaining of a delay of eighteen days. Physical examination was negative. Pelvic examination: uterus was small but slightly softened. There was some tenderness, but not marked, in the right adnexa. Aschheim-Zondek test was positive (September 20). On September 15 and 16 she received injections of 1 c.c. of prostigmine. She spotted approximately seventeen hours after the last injection, and the tenderness on the right side seemed to be increased. Injections were discontinued for fear of ectopic gestation. Although the patient was told to report back to the clinic she did not, but indirectly it was heard that five days later she was operated upon for some emergency abdominal condition.

These four cases, therefore, must be classified as false negatives since all were gravid, yet bled after prostigmine had been administered. In Case 49, although the result of the Aschheim-Zondek test was not conclusive, both the subjective symptoms and the increased size of the uterus on bimanual examination left the distinct impression that pregnancy existed. The possibility of gravidity, therefore, must be admitted, together with the possibility of spontaneous abortion, or induced abortion as the result of the injections of prostigmine. However, none of the above assumptions can be definitely proved. In the second case (Case 65), although no Aschheim-Zondek test was performed, there was the definite impression that the patient was gravid. Although this patient bled similar to a normal menstruation, examination one month later definitely proved the original diagnosis, since the size of the uterus had increased to that of a nine or ten weeks' gravidity. In order to verify this, prostigmine was again administered, but without any resulting bleeding. Similarly in Case 47, bleeding followed injections despite the fact that the patient was pregnant. In Case 69, although proof is not definitely obtainable, it is assumed from the history, physical examination, and follow-up, that the patient had an ectopic pregnancy, despite which she bled after two injections.

#### SUMMARY

Prostigmine methylsulfate successfully differentiated early pregnancy from temporary amenorrhea by inducing delayed menstrual flow in about 87 per cent of 90 cases that were thus tested. Patients were not selected and no distinction as to menopausal state, endocrine status, pelvic pathology, etc., was made. Injections were given only to those patients who definitely requested an opinion as to whether or not they

## CONSERVATIVE TREATMENT OF PELVIC INFLAMMATION WITH THE NEWMAN THERMO-FLO

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THE incidence of pelvic inflammatory disease in a gynecologic clinic is high. It is also an important factor, contributing to chronic ill health so frequently seen in this group of women, and it often forms a basis for such common complaints as abdominal pain, backache, dysmenorrhea, menstrual irregularity, vaginal discharge and the neurasthenic syndrome. Whatever plan of treatment is employed, the conservative management of pelvic inflammation merits most careful consideration, first, because of good results that have been reported by the use of various conservative measures, and second, because of the danger and unsatisfactory results that frequently follow more radical operative intervention.

Heat applied to the pelvis as a therapeutic measure has been used in various forms since the time of Hippocrates who described the simple hot vaginal douche. Other methods subsequently introduced include, heated lead shot poured into the vagina as described by Holden and Gurnee,<sup>1</sup> the hot intravaginal douche which was condemned by Emmet,<sup>2</sup> the prolonged vaginal douche as described by Gellhorn,<sup>3</sup> the Elliott apparatus, diathermy, and short wave therapy.

Newman,<sup>4</sup> in 1939, described the thermo-flo, which marks a definite advance in the application of intravaginal heat. This apparatus was used in our work in the treatment of pelvic inflammatory conditions at the Cook County Hospital and the Research and Educational Hospital, Chicago. It was proved to be an effective, yet simple and safe, device, and free from the objections which have been raised against the other methods.

Falls, Newman, and Kobak<sup>5</sup> published a preliminary report on the use of this apparatus on gynecologic patients at Research and Educational Hospital and Cook County Hospital, which was read in September, 1939, at the American Congress of Physical Therapy, in New York City. In general, the results in this series of 71 cases correspond with those obtained in the series here reported.

Greenhill<sup>6</sup> states that he has used the Newman thermo-flo successfully in the treatment of pelvic inflammatory disease.

this drug, with its diagnosis dependent upon the resumption of menstrual function, will keep a great many women from unnecessary manipulations at the hand of the abortionist. Furthermore, the resumption of the normal menstrual rhythm in the nonpregnant is a great psychological factor, especially when pregnancy is not desired at the time that the menses is delayed.

The use of prostigmine methylsulfate as a therapeutic measure for the regulation of the menstrual rhythm has not as yet been fully examined and studied. However, its field of usefulness would seem to be here, rather than in the field of diagnosis. Further experimentation is now in progress to determine the exact nature and physiology of this drug on the female generative tract.

#### CONCLUSIONS

Prostigmine methylsulfate was successfully used in the differentiation of amenorrhea due to pregnancy from amenorrhea due to other causes in 86.6 per cent of 90 cases. Diagnostic errors occurred in both pregnant and nonpregnant cases. Four patients who were pregnant bled; 10 continued their amenorrhea despite nongravity. Although statistical results are favorable, because of the possible abortion factor, prostigmine should not be used where pregnancy is urgently desired, where relative sterility existed, where a history of repeated abortions is elicited, or when pseudocyesis is present. These contraindications, together with those mentioned in previous publications, namely, endocrine dysfunction, local pelvic changes, possible ectopic pregnancy, menopause, etc., make the drug, as a diagnostic procedure, of extremely small value. Prostigmine, however, is of real worth as a therapeutic measure in temporary amenorrhea after the diagnosis of nongravity has already been established.

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1045 PARK AVENUE

freedom from potential burns and complete comfort during treatment are a few of the important advantages of the Newman thermo-flo apparatus.

Adair,<sup>7</sup> reporting the work done with this apparatus at the Chicago Lying-in Hospital, states that among the advantages of the thermo-flo may be mentioned the extremely simple mechanism, the ease and rapidity of its operation, and most important, the greater comfort afforded the patient.

Counsellor<sup>8</sup> objects to the use of a nondistensible electrode in the vagina because the rugae or folds prevent even distribution of heat and render the vaginal mucosa more susceptible to burns.

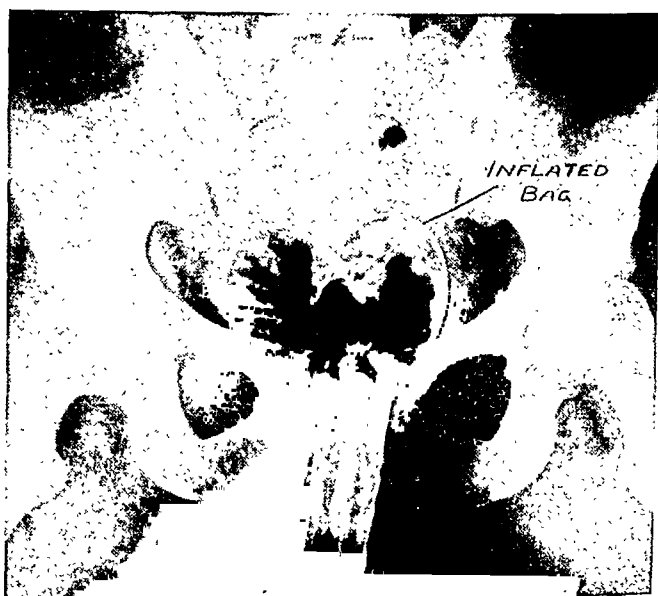


Fig. 2.—Roentgenograph of pelvis showing inflated rubber bag in the vagina.

Fig. 2 shows roentgenologically the position of the inflated bag in the vagina.

#### PHYSIOLOGIC EFFECTS OF LOCAL HEAT

When heat is applied locally to the body, the increased blood and lymph circulation due to dilatation of the arteries, arterioles, and capillary bed, is chiefly responsible for the desired therapeutic effect. If the process is kept within physiologic limits, tissue injury will not result. Increased circulation through the tissues promotes tissue metabolism, augments oxygenation of the cells, and hastens the exchange of the metabolites.

Bier<sup>9</sup> called attention to the value of producing active hyperemia by means of heat for the destruction of an infective process.

Michel and Taube,<sup>10</sup> in reporting upwards of 1,000 cases treated with pelvic heat, are of the opinion that any heat capable of being applied

## DESCRIPTION OF APPARATUS

The Newman thermo-flo apparatus (Fig. 1) as a simple device for the application of intravaginal heat, utilizes circulating air as the heating medium and in this respect differs fundamentally from other methods. Essentially, the apparatus is composed of a motor-driven fan which circulates heated air that is applied to the pelvis by means of a bicornuate-

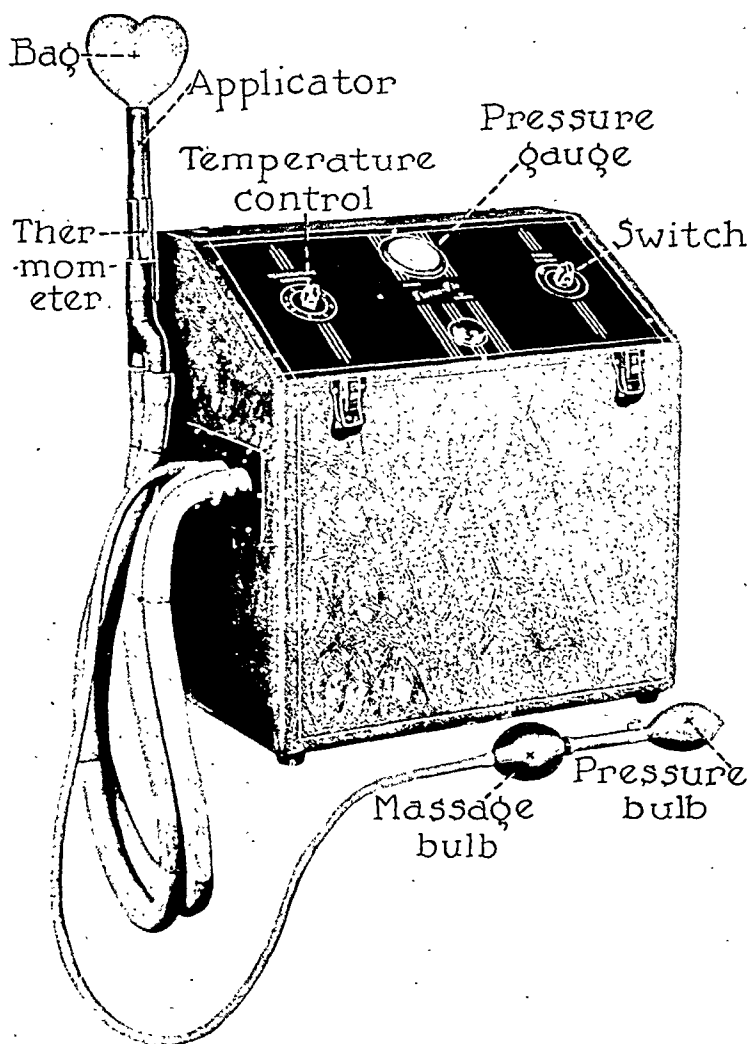


Fig. 1.—Newman thermo-flo.

shaped, inflated, thin rubber applicator bag. Temperatures up to 132° F. are automatically maintained by thermostatic control and registered by a thermometer extending into the applicator bag. The air pressure within the distended bag is regulated by means of a rubber bulb and is indicated on the pressure gauge. Uniform distribution of heat over a large surface of the vagina, negligible weight of an air-filled bag, relative



Cases designated as markedly improved include patients with absolute symptomatic relief in most cases, and marked, though not complete, regression of tangible pathologic findings.

Cases designated as moderately improved include those with satisfactory symptomatic relief even in the presence of definite pathologic changes.

Cases designated as slightly or not improved include those with some symptomatic relief but little or no alteration in the pathology present.

*Gonococcal Infections.*—This major classification was further subdivided according to the degree and extent of pathologic involvement of the pelvic structures. This varied from mild bilateral salpingo-oophoritis

## TOTAL 200 CASES

141 CASES. 70.5%

COMPLETE CURE or  
MARKED IMPROVEMENT

**44** CASES. 22.0%

MODERATE IMPROVEMENT

**15** CASES. 7.5%

SLIGHT or NO IMPROVEMENT

Fig. 3.—Results of 200 cases of pelvic inflammatory disease treated with the thermo-flo.

with pelvic peritonitis, to those of more severe nature with purulent salpingitis and tuboovarian abscess, and finally to the extensive and diffuse, exudative, pan-pelvic peritonitis known as the "frozen pelvis."

Our first series included 87 cases of bilateral salpingo-oophoritis (Table I); of these 75 were chronic: 12 were subacute. Chronicity was designated, if the symptoms and findings persisted for three months or longer. In these groups, 51 patients were white, 36 colored. The duration of symptoms varied from three months to thirteen years, and the age incidence averaged twenty-five years. The number of thermo-flo treatments per patient varied from 6 to 32, with an average of 14. Eight cases were classified as completely cured; 54 as markedly improved; 18 as moderately improved and 7 as slightly or not improved. It is interesting to note that 5 of the 8 patients classified as completely cured, subse-

without damage to the tissues kills only the organisms which come in direct contact with the applicator, and that the organisms deep in the tissues are only attenuated, so that their destruction is more easily accomplished by the normal defense mechanism.

Locally, there is noted a marked increase in phagocytic leucocytes and more rapid absorption of inflammatory exudates. A general leucocytosis is also produced after treatment in most cases, an average increase of 18 per cent.

#### CLINICAL RESULTS

We have observed in our series, 200 cases of pelvic inflammatory disease, which were classified as accurately as possible, into three major groups. This classification is based upon the information obtained from the history, physical findings, and bacteriologic studies in the individual cases.

##### I. Gonococcal infections. This included:

- A. Chronic bilateral salpingo-oophoritis.
- B. Chronic bilateral salpingo-oophoritis with unilateral or bilateral tuboovarian masses.
- C. Chronic diffuse pelvic inflammatory disease, the so-called "frozen pelvis."

Most of the patients in this gonococcal series present a history of one or more exacerbations of their pelvic infection over a varying period of time.

##### II. Nonspecific pelvic infections.

This included primarily the puerperal and septic-abortion cases, caused mainly by the streptococcus.

- A. Chronic pelvic cellulitis, parametritis and tubo-oophoritis.

##### III. Postoperative residual pelvic inflammatory disease. This included both the gonococcal and nonspecific groups.

We have classified the clinical results of treatment into four groups, namely: Complete cure, marked improvement, moderate improvement and slight or no improvement (Fig. 3).

The criteria used for classification included an accurate appraisal of symptomatic improvement stated by the patients and frequent check-up examinations of the pelvis, in most instances by the same clinician. The latter anatomic findings were mainly stressed in this analysis. The factors used in making this clinical classification, to indicate improvement, included lessened or absent tenderness, diminution in size of inflammatory masses, resolution of broad ligament thickening and induration, and increased mobility of the pelvic structures.

Cases designated as completely cured include those with absolute symptomatic relief and apparently complete regression of tangible pathologic findings.

TABLE III. CHRONIC PELVIC INFLAMMATORY DISEASE (FROZEN PELVIS), 12 CASES

| NO. OF CASES | AGE                    | DURATION OF SYMPTOMS | NO. OF TREATMENTS | COMPLETE CURE | MARKED IMPROVEMENT | MODERATE IMPROVEMENT | SLIGHT OR NO IMPROVEMENT |
|--------------|------------------------|----------------------|-------------------|---------------|--------------------|----------------------|--------------------------|
| 12           | 20 to 42 yr.<br>Av. 30 | 3 mo. to 8 yr.       | 9 to 18<br>Av. 14 | 0             | 8                  | 4                    | 0                        |

of 14. Seven patients were white and 5 colored. In one instance a pelvic abscess was drained through a posterior colpotomy incision. One patient was subsequently operated upon because of associated fibromyomas and protracted menorrhagia. Eight cases were classified as markedly improved and 4 as moderately improved.

*Nonspecific Pelvic Infections.*—This classification comprised postabortal, postpartum, and postoperative (Cesarean section) cases, primarily streptococcal in origin (Table IV), a total of 35 cases.

TABLE IV. PARAMETRITIS (POSTABORTAL, POSTPARTUM, POSTOPERATIVE), 35 CASES

|          | NO. OF CASES |            |               | AGE      | DURATION OF SYMPTOMS | NO. OF TREATMENTS | COMPLETE CURE | MARKED IMPROVEMENT | MODERATE IMPROVEMENT | SLIGHT OR NO IMPROVEMENT |
|----------|--------------|------------|---------------|----------|----------------------|-------------------|---------------|--------------------|----------------------|--------------------------|
|          | POSTABORTAL  | POSTPARTUM | POSTOPERATIVE |          |                      |                   |               |                    |                      |                          |
| Acute    | 8            | 1          | 1             | 17 to 40 | 1 wk. to             | 7 to 27           | 0             | 7                  | 3                    | 0                        |
| Subacute | 7            | 0          | 2             | yr.      | 5 yr.                | Av. 14            | 1             | 6                  | 2                    | 0                        |
| Chronic  | 7            | 8          | 1             | Av. 27   |                      |                   | 1             | 8                  | 3                    | 4                        |
| Total    | 22           | 9          | 4             |          |                      |                   | 2             | 21                 | 8                    | 4                        |

This series included 24 cases of septic abortion, 8 of which were acute, 7 subacute and 7 chronic; 9 cases followed full-term delivery and 4 cesarean sections. The duration of symptoms varied from one week to five years; the age incidence from 17 to 40, an average of 26.5 years. The number of thermo-flo treatments varied from 7 to 27, averaging 14. Twenty-two patients were white and 13 colored. Of this group, 2 became pregnant following treatments. In two instances a pelvic abscess was drained per vaginam. One postoperative case, following a total hysterectomy for fibroids and chronic cervical pathology, developed a fulminating, rapidly spreading cellulitis which responded favorably to heat treatments. Two cases were classified as completely cured; 21 as markedly improved; 8 as moderately improved and 4 as slightly or not improved. Generally speaking, regression of the pathologic changes in this group appeared to be more complete in the severe cases than was noted in those of gonococcal origin.

*Postoperative Residual Pelvic Inflammatory Disease.*—This classification included both the gonococcal and nonspecific groups, in which operation was previously performed on one or more occasions for such infections (Table V).

This series of postoperative residual pelvic inflammatory disease consisted of 33 cases; 29 of which were chronic and 4 subacute. The duration of symptoms varied from four months to eight years; the age incidence was from twenty-four to forty-six, an average of 32.5 years. The number of thermo-flo treatments varied from 9 to 55, averaging 17.

TABLE I. BILATERAL SALPINGO-OOPHORITIS; 87 CASES

|          | NO.<br>OF<br>CASES | AGE           | DURATION<br>OF<br>SYMPTOMS | NO. OF<br>TREAT-<br>MENTS | COM-<br>PLETE<br>CURE | MARKED<br>IM-<br>PROVE-<br>MENT | MODER-<br>ATE IM-<br>PROVE-<br>MENT | SLIGHT<br>OR NO<br>IM-<br>PROVE-<br>MENT |
|----------|--------------------|---------------|----------------------------|---------------------------|-----------------------|---------------------------------|-------------------------------------|--|
| Subacute | 12                 | 17 to 56      | 2½ mo. to                  | 6 to 32                   | 2                     | 7                               | 2                                   | 1  |
| Chronic  | 75                 | yr.<br>Av. 25 | 13 yr.                     | Av. 14                    | 6                     | 47                              | 16                                  | 6  |
| Total    | 87                 |               |                            |                           | 8                     | 54                              | 18                                  | 7  |

quently became pregnant after sterile periods of two to four years. One patient who was subsequently operated upon because of complaints referable to a retroversion was found to have patent tubes on retrograde insufflation. It was observed during the course of treatment for the upper pelvic tract infections that many cervical erosions became healed. The complication of gonococcal arthritis was noted once in this series, during the course of a subacute exacerbation of the pelvic infection, in a negress.

Our second series included 33 cases of bilateral salpingo-oophoritis with unilateral or bilateral tuboovarian masses (Table II). Of these 29

TABLE II. BILATERAL SALPINGO-OOPHORITIS WITH UNILATERAL OR BILATERAL TUBO-OVARIAN MASSES, 33 CASES

|          | NO.<br>OF<br>CASES | AGE           | DURATION<br>OF<br>SYMPTOMS | NO. OF<br>TREAT-<br>MENTS | COM-<br>PLETE<br>CURE | MARKED<br>IM-<br>PROVE-<br>MENT | MODER-<br>ATE IM-<br>PROVE-<br>MENT | SLIGHT<br>OR NO<br>IM-<br>PROVE-<br>MENT |
|----------|--------------------|---------------|----------------------------|---------------------------|-----------------------|---------------------------------|-------------------------------------|--|
| Subacute | 4                  | 17 to 52      | 2 mo. to                   | 6 to 26                   | 0                     | 2                               | 1                                   | 1  |
| Chronic  | 29                 | yr.<br>Av. 26 | 10 yr.                     | Av. 16                    | 0                     | 22                              | 5                                   | 2  |
| Total    | 33                 |               |                            |                           | 0                     | 24                              | 6                                   | 3  |

were chronic; 4 subacute. The duration of symptoms varied from two months to ten years; the age incidence averaged 26 years. The number of thermo-flo treatments per case varied from 6 to 26, average 16. The group includes 21 white, and 12 colored patients. It will be noted that there were no cases classified as complete cure in this group based on pathologic findings. The majority (24), however, were classified as markedly improved; 6 as moderately improved and 3 cases as slightly or not improved. Two patients with tuboovarian abscesses were drained per vaginam and then given thermo-flo treatments. Six patients were operated upon because of inadequate response to therapy and for economic reasons. One of these cases with moderately advanced adnexal pathology and retroversion received a course of 8 preoperative treatments and at operation the adnexa appeared sufficiently normal to warrant their retention. A uterine suspension operation was performed.

Our third series included 12 cases of chronic pelvic inflammatory disease, "frozen pelvis" (Table III). In this group the duration of symptoms varied from three months to eight years; the age incidence varied from twenty to forty-two years, an average of 30 years. The number of thermo-flo treatments varied from 9 to 18, with an average

time to draw conclusions, we feel that thermo-flo treatment can be advocated as a safe procedure and a real adjuvant in the therapy of such conditions. The results of a much larger group of similar cases as yet unpublished, tend to fully support these views. The pelvic heat therapy, together with the sulfonamide drugs, has made the clinician somewhat less fearful in the management of these severe streptococcal infections of the pregnant uterus.

The clinical course of these cases as contrasted to the gonococcal group, appears to be much more rapid in most instances, with a more complete resolution of pelvic pathology. In this group, particularly the acute and subacute cases, treatment once or twice daily for one hour is advocated, especially during the patient's hospital stay. At present, we are cautiously extending the indication for heat treatment to include a study of prolonged intravaginal heat application, from eight to twelve hours, particularly in the more severe septic cases.

The series designated as postoperative residual pelvic inflammation contained many cases in which conservative surgery had been practiced, with resultant residual pathology. Exacerbations or external reinfections were frequently responsible for the recurrent clinical manifestations. Many patients possess the inherent tendency to develop abundant adhesions. We feel that the intravaginal heat may have aided these patients by stimulating pelvic circulation and causing a resorption of the residue.

It was noted in the course of treatment of many of these cases that concomitant bladder and rectal infections were clinically improved. The location of these organs makes possible their inclusion in the exposure to heat in the distended vagina.

In many instances of sterility, when tubo-oophoritis is a predominant causative factor, we feel that a trial of intravaginal heat therapy is warranted. In our series, 7 patients with previous histories of sterile periods of from two to four years, became pregnant after a series of thermo-flo treatments. Although this is not a large group, we feel justified in advocating this conservative measure, since surgical tubal reconstruction is rarely successful.

Intravaginal pelvic heat therapy is not advocated as a panacea for the cure of all types of pelvic infections. We present it as a definite improvement in the manner of heat application in the conservative management of many of these cases. It must be realized, because of the varied pathology in many cases, as well as associated complicating pathology, that operative intervention will be the treatment of choice in some instances.

#### SUMMARY

1. The Newman thermo-flo apparatus, in our hands, has proved an effective method for the application of prolonged intravaginal heat. The

Sixteen of the patients were white and 17 colored. One case was classified as completely cured, 23 as markedly improved, 8 as moderately improved, and 1 as slightly or not improved.

One patient was subsequently re-operated upon for an old broad ligament hematoma. Another received a series of 12 thermo-flo treatments and at subsequent operation an infected ovarian cyst was removed.

TABLE V. POSTOPERATIVE RESIDUAL PELVIC INFLAMMATORY DISEASE, 33 CASES

|          | NO.<br>OF<br>CASES | AGE           | DURATION<br>OF<br>SYMPTOMS | NO. OF<br>TREAT-<br>MENTS | COM-<br>PLETE<br>CURE | MARKED<br>IM-<br>PROVE-<br>MENT | MODER-<br>ATE<br>IM-<br>PROVE-<br>MENT | SLIGHT<br>OR NO<br>IM-<br>PROVE-<br>MENT |
|----------|--------------------|---------------|----------------------------|---------------------------|-----------------------|---------------------------------|--|--|
| Subacute | 4                  | 24 to 47      | 4 mo. to 8                 | 9 to 55                   | 0                     | 4                               | 0                                      | 0  |
| Chronic  | 29                 | yr.<br>Av. 33 | yr.                        | Av. 17                    | 1                     | 19                              | 8                                      | 1  |
| Total    | 33                 |               |                            |                           | 1                     | 23                              | 8                                      | 1  |

### DISCUSSION

Although difficult to prove statistically, gonorrheal infection in the female pelvis is the most common cause of serious pathology, and is frequently productive of marked physical disability and sterility in the female. In recent years many authors have stressed the advantages of conservative management of pelvic inflammatory disease. From our experience we feel that the use of this form of intravaginal heat should definitely be added as an important factor in such management. We also feel that this form of treatment is a definite adjuvant pre- and post-operatively, particularly for the more extensively involved cases. Certainly, in those cases which subsequently come to operation, the quiescent phase of pelvic infection produced by this method of heat application produces definite decrease in morbidity and mortality.

Many of the patients seen at large charitable institutions, such as the ones from which this study was obtained, must, of economic necessity, be quickly restored to good physical health. Hence, surgical intervention is practiced much more freely than in other economically more independent strata of society. These factors played an important role in determining operative intervention in many of the 17 surgical cases in our series.

It is of great importance that chronic foci of infection in the lower genital tract be adequately treated in conjunction with the conservative treatment of the upper pelvic infection, to minimize the danger of auto-reinfection. Unless there exist pressing indications for immediate operation in pelvic inflammatory disease, we suggest a trial period of conservative treatment for three months; twice or three times weekly, in practically all cases, before surgery is contemplated.

Some months ago, we decided to try intravaginal heat therapy in the treatment of puerperal infection, including postabortal, post-partum and postoperative cases. Although our series is not large enough at this

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## VAGINAL IONTOPHORESIS OF A CHOLINE COMPOUND\*

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A STUDY of vaginal iontophoresis of a choline compound was begun in 1933 to determine whether any beneficial effects could be produced by its use in cases of pelvic inflammation. Two previous communications by one of us have appeared in the literature,<sup>1, 2</sup> detailing the results obtained in a limited number of patients. Since then, reports by others,<sup>3, 4</sup> to whom we demonstrated this modality, have already been or are about to be published, which substantiate our original conclusions. Since our last publication, we have amplified our observations on patients with pelvic inflammation and have also had occasion to add other groups in this survey: those in whom diagnostic clarification was necessary, patients with ovarian cysts, and a number complaining of dysmenorrhea.

The original technique has already been described in detail.<sup>1, 2</sup> The only recent change made is in the strength of the mecholyl solution employed. We are now using a 0.25 per cent solution of mecholyl instead of a 0.5 per cent solution, with equally satisfactory results. This can be readily understood, because the amount of mecholyl driven into the tissues is entirely dependent upon the strength of the current and the duration of its flow. In the technique now used which permits 15 milliamperes of current to flow for twenty minutes, only a portion of the material in the 0.25 per cent solution is utilized, so that even further dilutions might still produce satisfactory results. We have not yet encountered any instance of shock during treatment which has required interruption of the treatment and the administration of atropine to counteract the mecholyl effect. The results obtained in a group of patients with acute or chronic pelvic inflammatory disease are shown in Table I.

\*Mecholyl, a product of Merck & Co., Rahway, N. J.

method utilizes heated air and presents advantages over other devices, because of simplicity of operation, comfort, freedom from potential burns, and because it gives uniformly effective application of pelvic heat.

2. Two hundred patients with pelvic inflammatory disease were treated with the thermo-flo, of whom 141 (70.5 per cent) showed complete cure or marked improvement; 44 (22 per cent) moderate improvement, while 15 (7.5 per cent) obtained slight or no improvement. (a) Gonococcal infections in 132 cases showed in 94 (71.2 per cent) complete cure or marked improvement; in 28 (21.2 per cent) moderate improvement; and in 10 (7.6 per cent) slight or no improvement. (b) Nonspecific pelvic infection observed in 35 cases produced in 23 (65.7 per cent) complete cure or marked improvement; 8 (22.9 per cent) moderate improvement, and 4 (11.4 per cent) slight or no improvement. (c) Postoperative residual pelvic inflammatory disease seen in 33 cases yielded 24 (72.7 per cent) completely cured or markedly improved; 8 (24.2 per cent) moderately improved; and 1 case (3.1 per cent) slightly or not improved.

3. Seven patients of the entire series presented additional complaints of sterile periods of two to four years and subsequently conceived after thermo-flo treatments.

4. Bladder and rectal inflammation associated with pelvic infection is favorably influenced by the use of intravaginal heat.

5. In cases of gonococcal, nonspecific, and postoperative residual infections of the pelvis, our clinical impression was that a more rapid and complete resolution of pathology and improvement of clinical symptoms takes place, in a shorter period of time, than with previous methods of treatment.

6. We recommend the use of intravaginal heat therapy (thermo-flo) as a pre- and postoperative measure, in suitable cases.

7. We wish to emphasize that the treatment of pelvic inflammatory disease by intravaginal heat (thermo-flo) does not replace operative therapy in all instances, particularly when associated pelvic pathology exists. In a large group of society, surgery is more frequently indicated because of economic dependency.

We are greatly indebted to Esther Stumbo, R.N., Chief Physical Therapist, Cook County Hospital, Chicago, for her aid in this work.

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TABLE II. OPERATIVE CASES

| CHRONIC PELVIC INFLAMMATION |   |   |               |  |  |                          |
|-----------------------------|---|---|---------------|--|--|--------------------------|
| NO.                         | DIAGNOSIS   | PREOPERATIVE FINDINGS   | IONTOPHORESIS | OPERATION  | PATHOLOGY  | LATE FOLLOW-UP           |
| 1                           | Left salpingo-oophoritis; fibroid uterus                              | Intramural fibroid; left fornix filled with doughy, cystic, tender mass                         | 1 month       | Left ovary resected; adhesions liberated                                 | Intestinal adhesions to left broad ligament and ovary; gigantic corpora fibrosa left ovary   | 1934, no improvement     |
| 2                           | Left salpingo-oophoritis  | Left fornix filled with large hard mass, possible dermoid                                       | 2 weeks       | 1936, left tube and ovary resected; right tube, fimbriated end, resected | Omentum adherent to left tube and ovary. Ovary 3 inches in diameter. Cystic. Fimbriated end right tube closed                              | 1940, cured tube patient |
| 3                           | Bilateral salpingo-oophoritis. Third-degree reversion; fibroid uterus | Right fornix filled with large cystic mass; left ovary cystic; uterus retroverted; hard, knobby | 1 month       | 1937, ovary suspended; fibroid enucleated                                | Uterus bound down in cul-de-sac; fibroid; right ovary normal. Left recent rupture Graafian follicle; tubes showed evidence salping-nodosum | 1941, improved           |
| 4                           | Left tuboovarian mass. Metastatic carcinoma left ovary with infection | Mass in left fornix 4 inches in diameter  | 3 months      | 4/28/38, bilateral salpingitis; left oophorectomy; resection sigmoid     | Ovary, serous cysts; tube showed scarring; bowel adenocarcinoma  | Infection cured          |
| 5                           | Bilateral salpingo-oophoritis   | Soft, tender mass filling right fornix to pelvic wall. Left tube and ovary thick and tender     | 6 weeks       | 8/4/36, adhesion freed; uterus suspended. Appendectomy                   | Uterus retroverted and to left. Left tube and ovary normal; right tube normal. Adhesions between right ovary and right broad ligaments     | Cured                    |

TABLE I. ACUTE AND CHRONIC PELVIC INFLAMMATORY DISEASE, NONOPERATED (74)

| TYPE   | NO. | FIRST WEEK |                        | FIRST MONTH |                     | LATE FOLLOW-UP<br>1-7 YEARS |         |           |
|--|-----|------------|------------------------|-------------|---------------------|-----------------------------|---------|-----------|
|  |     | RELIEF     | SLIGHT OR<br>NO RELIEF | IMPROVED    | NO IMPROVE-<br>MENT | CURED                       | NO IMP. | NOT FOUND |
| Bilateral salpingo-oophoritis<br>with parametritis | 38  | 36         | 2                      | 33          | 5                   | 28                          | 3       | 7         |
| Bilateral salpingo-oophoritis<br>with retroversion | 4   | 2          | 2                      | 4           |                     | 3                           | 1       |           |
| Unilateral salpingo-oophoritis                     | 25  | 20         | 5                      | 24          | 1                   | 19                          | 1       | 5         |
| Parametritis                                       | 7   | 7          |                        | 6           | 1                   | 6                           | 1       |           |
| Total  | 74  | 65         | 9                      | 67          | 7                   | 56                          | 6       | 12        |
| Per cent   | 100 | 87.8       | 12.2                   | 90          | 10                  | 75.6                        | 8.1     | 16.3      |

In all of these patients the results were evaluated by the subjective symptoms and the changes found on physical examination after treatment. Except in patients suffering from acute pelvic inflammation and pyrexia, the treatment was administered as an ambulatory procedure.

In this group of 74 patients, a striking effect was the rapid lessening of the patient's complaints, and these changes were noticeable within the first week. A follow-up on this group, in some instances as long as seven years after treatment, showed that of the 62 patients contacted, 90.3 per cent remained cured. The cure in this group consisted of the complete disappearance of all inflammatory exudate, and in the majority, restitution of the affected organs to normal. In 18 of the 56 patients considered cured, a slight residual thickening remained.

In an additional group of 11 patients with inflammatory adnexal involvement, operation was performed after varying periods of preliminary treatment by iontophoresis. The details of this group are set forth in Table II. There was no apparent improvement in only one of these patients re-examined later.

The group in which treatment was instituted for the diagnostic clarification of the nature of palpable pelvic masses included 17 patients. Nine of these patients were operated upon subsequent to therapy. The other 8 did not require or refused operation, and the details are set forth in Table III, A and B. In these 8 patients re-examined after a course of therapy, the residual pathology was determined by physical examination and the extent of change in the pelvic masses noted. In the 9 patients who were subjected to operation, actual visual evidence was available. It was noticeable that when inflammatory pelvic disease complicated coexisting noninflammatory pathology, the operative procedures were rendered considerably less difficult and extensive by the prior reduction of the inflammatory process.

A group of 17 patients diagnosed as having various types of ovarian cystoma was subjected to treatment for variable periods as indicated in Table IV. The results obtained were not uniform. In some instances, the cystic areas in the ovaries apparently disappeared. In 4 patients, subsequently operated upon, the variable outcome following treatment was confirmed, as the enlargements of the ovary consisting

TABLE III A. FOR CLARIFICATION OF DIAGNOSIS IN PELVIC TUMEFACCTIONS

| NO. | DIAGNOSIS  | IONTO-PHORESIS       | POSTTHERAPY FINDINGS   | FINAL DIAGNOSIS                          | RESULT               |
|-----|--|----------------------|--|--|----------------------|
| 1   | Fibroid uterus; possible inflammatory mass   | 1 month              | Uterus irregular; enlarged; hard; fibroid  | Fibroid                                  | None                 |
| 2   | Parametritis; probable nonsurgical fibroid; left salpingitis; bilateral oophoritis | 5/5/39,<br>1 month   | 6/39, right ovary normal; left ovary prolapsed normal. Uterus normal. No evidence parametritis       | Pelvic inflammatory disease              | 1/9/40,<br>cured     |
| 3   | Dextroretroverted uterus; probable fibroid uterus; coccygodynia                    | 6/13/39,<br>1 month  | Uterus normal; all fornices clear  | Pelvic inflammatory disease              | 6/20/40,<br>cured    |
| 4   | Fibroid uterus; bilateral adnexal disease  | 9/11/37,<br>2 months | Right and left adnexal regions clear. Uterus in midline irregular, enlarged by fibroid in left cornu | Fibroid with pelvic inflammatory disease | 12/4/37,<br>improved |
| 5   | Parametritis; fibroid uterus   | 5/14/40,<br>1 month  | All fornices clear; uterus normal  | Pelvic inflammatory disease              | 10/15/40,<br>cured   |
| 6   | Possible fibroid, left parametritis  | 2/11/41,<br>1 month  | Small fibroid 1 inch in diameter. Left cornu. All fornices clear                                     | Fibroid with pelvic inflammatory disease | 3/11/41,<br>improved |
| 7   | Left parametritis; fibroid uterus  | 2/20/41,<br>1 month  | Small sessile fibroid in left border of uterus. Fornices clear                                       | Fibroid with pelvic inflammatory disease | 3/25/41,<br>improved |
| 8   | Fibroid uterus; cystic oophoritis  | 10/26/40,<br>3 weeks | All fornices clear; several small fibroids   | Fibroid                                  | 3/18/41,<br>none     |

|    |   | 10/16/34, right tubo-ovarian mass 3 inches in diameter. Left tube thick      | 3 months                                      | Colpotomy, 9/12/34   | Pelvis clear. Bartholini-an cyst   | 1940, cured       |
|----|---|--|---|--|--|-------------------|
| 6  | Acute bilateral salpingitis. Pelvic abscess; urethritis |  |   |  |  |                   |
| 7  | Left salpingo-oophoritis; parametritis                  | Tuboovarian mass left fornix; thickening in right fornix                     | 6 weeks. Returned 1 month. Right ovary cystic | 6/28/35, liberation of adhesions; right oophorectomy                                     | Left tube normal; left ovary adherent. Right tube normal; right ovary 4 inches in diameter | 9/12/35, cured    |
| 8  | Acute parametritis                                      | Marked thickening in all fornices  | 2 weeks                                       | 12/29/36, ten months later for acute appendicitis; partial resection left tube and ovary | Mild chronic salpingitis; corpora lutea of ovary   | 9/24/40, cured    |
| 9  | Bilateral salpingitis pyosalpingitis                    | Clubbed right mass behind uterus in cul-de-sac. Left mass 1 inch in diameter | 2½ months. Seemed to empty and refill         | 3/30/35, right salpingo-oophorectomy. Left salpingectomy                                 | Bilateral hydrosalpingitis. Right cystic ovary   | 4/24/41, cured    |
| 10 | Bilateral tuboovarian mass; fibroid uterus              | Uterus hard; irregular; enlarged; fornices filled with hard masses           | 6/7/38, 2 months. Masses cleared              | 5/28/40, 2 years later operation. Supravaginal hysterectomy. Liberation of adhesions     | Fibroid uterus; left tube and ovary necrotic; seat of abscesses                            | 5/10/41, improved |
| 11 | Right oophoritis  | Tender adherent right ovary  | 2 weeks improved                              | 7/11/39, 1 year later. Right oophorectomy; liberation of adhesions and appendectomy      | Adhesions; cystic right ovary  | 10/24/40, cured   |

TABLE IV. OVARIAN CYSTOMA

| NO.                | DIAGNOSIS  | IONTO-PHORESIS        | FINDINGS   | RESULT                              |
|--------------------|--|-----------------------|--|-------------------------------------|
| <i>Nonoperated</i> |  |                       |  |                                     |
| 1                  | Third degree retroversion; enlarged cystic right ovary | 10/20/36,<br>2 months | Uterus brought up.<br>Right ovary normal   | 1/26/37,<br>improved                |
| 2                  | Cystic cervicitis; bilateral cystic oophoritis         | 12/17/38,<br>4 months | Felt better. No physical change  | 9/21/40,<br>unchanged               |
| 3                  | Left ovarian cyst. Parametritis                        | 2/27/34,<br>1 month   | Left ovary prolapsed.<br>Normal  | 1/11/41,<br>improved                |
| 4                  | Bilateral ovarian cystoma                              | 11/4/39,<br>1 month   | Left ovary normal; right ovary unchanged after 10 months   | 9/1/40, improved one ovary          |
| 5                  | Right ovarian cystoma                                  | 10/20/38,<br>6 weeks  | Both ovaries normal  | 4/9/40,<br>improved                 |
| 6                  | Left ovarian cystoma. Retroverted uterus               | 1 week                | Uterus brought up. Both ovaries normal   | Improved                            |
| 7                  | Left ovarian cystoma. Right parametritis               | 1/28/39,<br>2 weeks   | Stopped treatment for 5 months. Returned. Cystoma increased in size  | 6/29/39,<br>unchanged               |
| 8                  | Pelvic exudate; right cystic oophoritis                | 6/16/36,<br>3 months  | Right ovary 1½ inches; cystic feel   | 1/30/40,<br>pelvis normal. Improved |
| 9                  | Left ovarian cystoma; retroverted uterus               | 9/1/38,<br>1 month    | No change  | 9/22/38,<br>unchanged               |
| 10                 | Bilateral cystic oophoritis                            | 5/4/39,<br>2 weeks    | Left ovary normal. Right slightly enlarged; returned 1 year later. Both ovaries normal   | 6/18/40,<br>improved                |
| 11                 | Left ovarian cystoma; left parametritis                | 11/12/35,<br>1 week   | Left ovary normal. Induration gone   | 10/13/39,<br>improved               |
| 12                 | Right cystic oophoritis; right parametritis            | 2/1/41,<br>1 month    | Pelvis normal; 2 months later pregnant   | 2/1/42,<br>improved                 |
| 13                 | Right cystic oophoritis; fibroid uterus                | 10/26/40,<br>2 weeks  | Both ovaries normal; fibroid uterus  | 3/18/41,<br>improved                |
| <i>Operated</i>    |  |                       |  |                                     |
| 14                 | Large right ovarian cystoma dermoid                    | 1/13/39,<br>5 months  | Dermoid. Right ovary removed   | 6/13/39,<br>improved                |
| 15                 | Left ovarian cystoma; peri-oophoritis                  | 5/19/38,<br>2 months  | 5/2/39, left ovary normal; returned 4 months later left ovary enlarged; operated for fibroid-ovary only 28 × 27 × 12 mm. Supravaginal hysterectomy and left oophorectomy | 7/39/40,<br>improved                |
| 16                 | Bilateral ovarian cystoma. Adhesions                   | 10/8/35,<br>3 months  | Left ovary normal (1/26/38); right slightly enlarged. Remained normal one year. Small cyst appeared in right fornix. One year later operated for left intraligament cyst | 9/24/40,<br>improved                |
| 17                 | Left ovarian cystoma; probable dermoid                 | 4 months              | 9/27/40, left oophoritis   | 4/1/41,<br>improved                 |

TABLE III B. FOR CLARIFICATION DIAGNOSIS IN PELVIC TUMEFACIONS (OPERATIVE CASES)

| NO. | DIAGNOSIS  | IONTO-<br>PHORESIS | OPERATION   | PATHOLOGY   | RESULT                                     |
|-----|--|--------------------|---|---|--|
| 1   | Fibroid uterus. Left salpingo-oophoritis                         | 2½ months          | 7/14/36, Liberation of adhesions. Left ovary resected   | Adhesions between intestine and ovary and left broad ligament. Corpus luteum cyst of ovary. Gigantic corpora fibrosa    | 4/1/37, improved                           |
| 2   | Fibroid uterus; bilateral salpingo-oophoritis. Cystic oophoritis | 2 weeks            | 4/30/37, Both ovaries suspended; 2 small fibroids enucleated. Appendectomy                      | Uterus bound by adhesions to intestine and omentum; fibroid on postuterine wall; both ovaries normal. Tubes appear open | 10/7/40, uterus reverted, otherwise normal |
| 3   | Intraligament cyst; fibroid uterus                               | 1 month            | 11/30/37, Myomectomy; appendectomy. 11/18/39, cesarean section                                  | 2 fibroids removed. Pregnancy   | 10/7/40, cured                             |
| 4   | Fibroid uterus; adhesions. Cystic right ovary                    | 1 week             | 1939, Right oophorectomy  | 2 small fibroids; right papilocystadenoma; adhesions  |  |
| 5   | Possible fibroid uterus; right salpingo-oophoritis               | 1 month            | 2/16/37, Supravaginal hysterectomy; right salpingo-oophorectomy. Appendectomy                   | Right ovary cystic. Normal size   | 6/28/38, cured                             |
| 6   | Fibroid uterus   | 1 month            | 7/20/40, Supravaginal hysterectomy; appendectomy. Adnexa retained                               | Fibroid   | 3/8/41, cured                              |
| 7   | Fibroid uterus. Bilateral tuboovarian masses                     | 2 months           | 9/27/40, Supravaginal hysterectomy. Partial removal of ovarian abscess. Liberation of adhesions | Fibroid uterus and left pyosalpingo-oophoritis  | 5/10/41, improved                          |
| 8   | Right tuboovarian mass; possible dermoid                         | 1 month            | 6/13/39, Right oophorectomy   | Right ovarian cyst 4 inches in diameter. Filled with fat and black hair   | Cured                                      |
| 9   | Carcinoma left adnexa and intestine. Exudate                     | 19 days            | 10/31/36, Biopsy  | Generalized adenocarcinoma  | No change                                  |

pelvic inflammatory disease. This observation led to the experimental treatment of dysmenorrhea in patients who were free from pelvic inflammation, and the results obtained are tabulated in Table VI. It is evident that when dysmenorrhea is caused by an associated pelvic inflammation, the pain is relieved as the pelvic inflammatory condition subsides. The results in patients with essential dysmenorrhea are too irregular to warrant the use of iontophoresis for its relief.

#### SUMMARY

As a result of nine years of experience with iontophoresis, we are convinced that the treatment is simple in application and practically free from any toxic reaction. Its greatest field of usefulness is in the treatment of inflammatory pelvic exudates. In such cases iontophoresis has made prolonged hospitalization unnecessary, has returned these women to usefulness, and has relieved symptoms much more quickly than is possible with other therapeutic methods. We now feel justified in stating that: (1) Mecholyl iontophoresis promptly cures exudative pelvic inflammation. (2) There is no effect on productive inflammatory pathology. (3) There is no effect on organized blood accumulations. (4) There is no effect on new growths, uterine, ovarian, or in other pelvic structures. (5) The therapy is a helpful differential diagnostic aid in pelvic masses. (6) Preliminary iontophoresis when associated inflammation exists renders operation easier and less extensive. (7) Certain follicular ovarian cysts are apparently influenced and disappear under therapy. (8) Dysmenorrhea associated with pelvic inflammation and caused thereby is relieved as the inflammation disappears, but primary or essential dysmenorrhea is unaffected in most instances.

From the foregoing, it is clear that iontophoresis is a safe, economic, rapid and practical therapeutic method for the relief of pelvic inflammation.

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151 WEST 77TH STREET  
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of new growths were not altered, whereas the recessions noted all appeared to be located in areas of follicular cystic disease. The reason for such a recession is not clear, although the possibility that improved circulation may stimulate the continuance of cyclic changes in the cystic accumulations may be the factor responsible for the disappearance of these cysts.

Four patients were treated for collections of blood in the pelvis more or less encapsulated (Table V). In none of these was very much change produced. It appears that organized blood accumulations undergo slow resolution and absorption, practically unaffected by extraneous factors.

TABLE V. HEMATOMA, ENCAPSULATED EXUDATE, ETC. (4)

| NO. | DIAGNOSIS  | IONTO-PHORESIS | RESULT  |
|-----|--|----------------|---|
| 1   | Probable pelvic hematocele following ectopic ruptured        | 3 months       | Small cystic area left, immediately behind and to left of uterus  |
| 2   | Left fornix exudate following hysterectomy                   | 3 months       | Mass grew large and more circumscribed with occasional bleeding per vaginam. Feels like a small piece of ovarian tissue   |
| 3   | Left intraligamentous exudate                                | 1 month        | Mass almost gone. Returned 2 years later. Mass 3 inches in diameter; treated about 5 months. No change. Stopped treatment. Returned 5 years later. Pelvis clear |
| 4   | Probably organized hematoma between leaves of broad ligament | 3 months       | Mass only slightly affected   |

## DYSMENORRHEA

It was noticed in the treatment of those patients with pelvic inflammation who concurrently suffered from dysmenorrhea that relief of the painful menstruation was coincident with the improvement in the

TABLE VI. DYSMENORRHEA (6)

| NO. | DIAGNOSIS   | IONTO-PHORESIS    | RESULT   |
|-----|---|-------------------|--|
| 1   | Dysmenorrhea; sterility. Acutely ante flexed uterus | Through 2 periods | No effect  |
| 2   | Dysmenorrhea  | 3 months          | Pain decreased with each period, until third period, when was free of all pain |
| 3   | Dysmenorrhea; left salpingo-oophoritis              | 1 month           | Pain, only slight  |
| 4   | Dysmenorrhea; left salpingo-oophoritis              | 6 weeks           | Pain gone; scant flow  |
| 5   | Dysmenorrhea  | 1 month           | No change. Subsequently operated for appendicitis. Now feels well              |
| 6   | Dysmenorrhea  | 2 weeks           | No relief  |



spayed animals. The normal ovary of the guinea pig seems to contain substances which in some way modify and diminish the tumor-producing action of estrogen. It was also found that male guinea pigs have a relatively much greater resistance to the tumorigenic action of estrogen.

Lipschutz observed that the production of tumors by injection or implantation of estradiol could be prevented or arrested by simultaneous injection of progesterone in comparative dosage. Testosterone was found to be even more effective as a tumor-preventive, and the most potent was the cortical hormone, "desoxycorticosterone."

Perloff and Kurzrok produced a fibromyoma in one uterine horn of a guinea pig by implantation of an estradiol pellet. No fibroid was produced in the other uterine horn by implantation of an identical pellet when testosterone was simultaneously implanted.

Since 1937 we have been trying to produce fibromyomas in animals. Several series of rats were injected for several months with large doses of estrone. At the same time an attempt was made to produce a local irritation of the uterus by implantation of foreign bodies and of small pieces of various other tissues. Like other investigators, we were unable to produce any fibromyomas in rats. Attempts to produce fibromyomalike tumors in unspayed guinea pigs were also unsuccessful in our hands.

During 1940 we spayed a series of 110 guinea pigs and injected them three times weekly for four months with large doses of estradiol-dipropionate. Approximately 5 mg. were used for each animal on which the experiment could be completed. On account of the seemingly increased susceptibility to infection of the estradiol-injected animals, and unfavorable laboratory conditions, only 12 animals survived. However, all the surviving guinea pigs showed multiple intra-abdominal tumors of fibromyomalike character. The majority of these tumors originated from the uterus. In 10 of the guinea pigs the tumors were on the uterine horns, mostly apical and subserous. In 9 they were also in the uterine body. Aside from these, there were many tumors extragenital in location. The parietal peritoneum of the anterior abdominal wall was involved in 8. In 2 cases they were located on the diaphragm, and one of these had pushed up into the thorax. The viscera were not excluded and tumors were found on the bladder, spleen, pancreas, and ilium.

The varied locations of these tumors, with a predilection for the uterus, corresponded with the findings of other investigators. Generally the tumors were round or oval, had a firm, rubbery consistency, a smooth contour, and thinned-out capsule.

Microscopically all the tumors were of similar character. They consisted largely of intertwining bundles of fibrous tissue, running in all directions without any relation to any structural and anatomic unit. Between these fibrous strands were larger or smaller groups of muscle cells. These muscle cells were larger and thicker than the normal ones,

# EXPERIMENTALLY PRODUCED FIBROIDS IN THE GUINEA PIG AND THEIR POSSIBLE ANALOGY TO MYOMAS IN THE HUMAN BEING\*

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FOR several years investigators have tried to produce uterine tumors in animals which could be compared to myomas in the human being.

In 1937 Nelson reported the production of fibromyoma-like nodules in the uteri of guinea pigs by prolonged administration of estrogens.

Moricard and Cauchoux produced fibromyomas in the female guinea pig by injection of estradiol benzoate. Lipschutz and Vargas have produced fibromalike abdominal tumors in guinea pigs by injection and implantation of estrogenic substances. They found that different estrogenic substances have a different growth-stimulating and tumor-promoting potentiality. They could increase the tumor-promoting action of estradiol in the guinea pig by esterifying it with certain acids, increasing its tumor-promoting potentiality up to 200 times by combining it with a certain isomer of caprylic acid. The uterine tissues not involved in the tumor formation were stimulated to a lesser degree to hyperplastic growth. The more continuously the estrogenic action was maintained, the more numerous and larger were the tumors produced. The longer the intervals between injections, the less tumor formation was obtained, no matter how great the potency of single injections. But even a relatively low level of estrogen stimulation was likely to produce tumors if it was maintained over a certain period of time, as by the implantation of pellets. No true parallelism was found to exist between the tumor-producing "tumorigenic" and the uterus-stimulating "hysterotrophic" action of different estrogenic principles.

The unpredictable tumor growth under the influence of estrogen on certain places within seemingly homologous tissues, and the dissimilar reaction of the surrounding tissues suggested that some less differentiated cells must be interspersed, which have a greater receptivity to growth stimulation. It is probable that these more responsive cells in the guinea pig are immature mesenchymal cells similar to those which Marchand and other investigators describe as "undifferentiated, perivascular, mesenchymal cells" persisting in the adult organism with the potencies of embryonic mesenchymal cells.

According to all investigators, it is more difficult and requires a much greater dosage of estrogen, to produce fibroids in guinea pigs in which the whole or a part of the ovarian tissue is retained, than it is in

\*The estradiol dipropionate used in these experiments was donated by the Ciba Company.

time of their production to the time of their excretion. They are esterified and neutralized by normal liver action and are excreted by the kidney. It can be assumed that these different fractions of the natural estrogens have also different effects on the various tissues of the organism in which they occur, and that some of their transitional phases may possess a relatively higher tumorigenic potentiality on receptive cells.

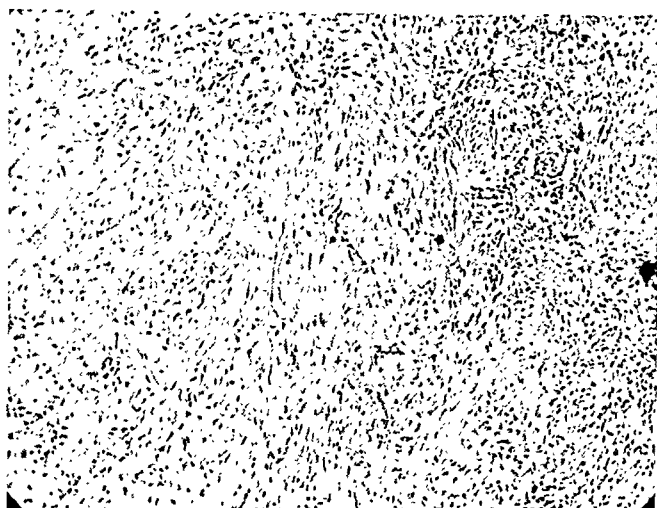


Fig. 2.—Section from medium-sized uterine tumor, low power.

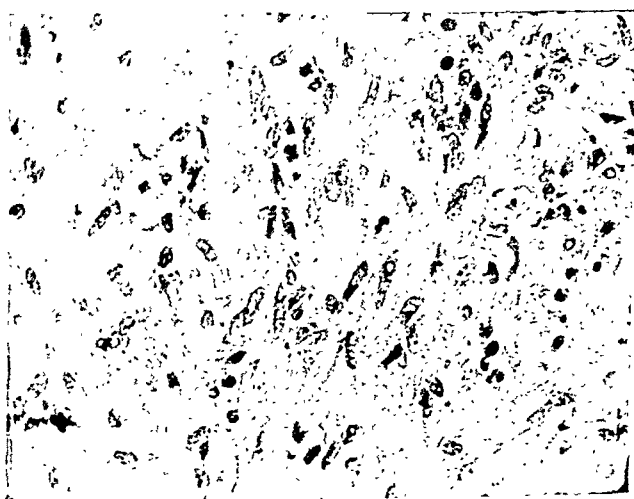


Fig. 3.—Section from medium-sized uterine tumor, high power.

There seems to be no direct chemical involvement of estrogen in the process of growth stimulation of myoma, in spite of its seemingly cumulative effect. But its action seems rather to be an indirect catalytic process. According to our own experiments there seems to be no storage of estrogen within the myomas. We made hormone assays of pieces of several human myomas and could not recover any appreciable amount

with a more granular cytoplasm. The nuclei were darker, larger, and more rounded.

In addition, there were occasional collections of fat and numerous round cells. In some places the pattern was very irregular and almost suggestive of sarcomatous changes. Mitotic figures were found frequently, but no invasion of the surrounding tissues was noted. Capillaries were present in abundance. The surface was usually composed of a capsule of flattened cells.

The question naturally arises: Is there any analogy between these experimental fibromyomas in guinea pigs and human myomas? We feel, with Lipschutz and Vargas, that these two types of tumors can be compared, in spite of their structural and biologic differences, when we make certain allowances for the dissimilar basic conditions under which the spontaneous and the artificial tumors are produced. One fact stands

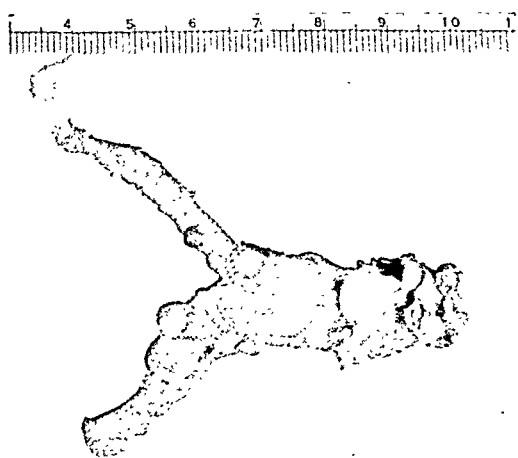


Fig. 1.—Multiple uterine tumors of guinea pig.

out which is valid for the etiology of all tumors: we cannot look for any single cause for their production; tumor growth is the result of a combination of favorable circumstances, the effect of the summation of various contributing factors.

Estrogenic substances, by being growth-stimulating, can become tumor-promoting if they can act in a certain quantity in sufficient intensity and over a certain period of time upon cells which are especially receptive; and if their action upon these cells is not balanced and neutralized by other protective substances.

In accordance with Lipschutz' observations, mentioned before, laboratory studies have shown that various natural and synthetic estrogenic substances affect different animal species in different degrees, and also different tissues of the same species in varying degrees. It is also known that several free and combined estrogenic fractions can be present in one organism at the same time, undergoing chemical changes from the

when there is a persistence of a comparatively even level of estrogen than when the estrogen fluctuates in normal cycles. In practice we find such conditions of protracted estrin stimulation in the presence of follicular retention cysts, which Witherspoon considers a primary cause of myoma. Following up the inference suggested by the experiments, persistence of even a moderate degree of estrin stimulation could more likely lead to myoma formation if it were accompanied by other ovarian or co-ordinated endocrine deficiencies. In such a case the estrogenic action would not be counterbalanced by other endocrine catalysts. Lack of endocrine equilibrium with a relative preponderance of certain estrogenic fractions could also explain the common association of sterility with myoma. Favoring such an occurrence would be the abundance of easily stimulated immature muscle elements in an under-developed uterus.

#### SUMMARY AND CONCLUSIONS

Lipschutz and several other investigators have produced fibromatous tumors in guinea pigs by protracted use of estrogenic substances. Retention of normal ovarian tissue or the simultaneous use of certain other endocrines inhibited the tumor formation. In our own experiments we were able to produce similar tumors in guinea pigs. In spite of histologic differences, certain analogies can be found between the genesis and production of experimental fibroids and human myomas. Both types of tumors originate from mesoblastic cells, the guinea pig fibroids seemingly from undifferentiated connective tissue cells, the human myomas from immature muscle cells. The growth of both tumors seems to depend upon estrogenic action when this is not counterbalanced by other growth-controlling catalysts.

By following up the apparent analogies between the data found in the experimental production of fibroids with the diverse factors thought responsible for the genesis of human myomas, we possibly can correlate some of these factors and come closer to an understanding of the etiology of myoma.

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of estrogenic substances, as likewise we failed to recover any in the normal uterine muscle wall.

The most commonly accepted theory of the histogenesis of the uterine myoma in women is the one advanced by Robert Meyer who claims that the myoma originates from immature muscle cells. Meyer found small seedlings of muscle cells in certain uteri grouped in dense bundles from  $\frac{1}{50}$  to  $\frac{1}{5}$  mm. in diameter, which he interpreted as incipient myomas.

Common to all uterine muscle cells is a special growth energy, as manifested by their special physiologic response to the stimulus of pregnancy. This growth potentiality is greater on the fundus than on the cervix, and the part which is capable of greater hypertrophy during pregnancy shows also greater potency to tumor formation.

A growing myoma, like other tumors, seems to attract its own blood supply from the adjoining vessels, stimulating the proliferation of capillaries; vice versa, the rate of growth of a tumor is influenced and limited by the available blood supply. It is well known that myomas are likely to grow during physiologic and pathologic states of the uterus which are accompanied by hyperemia, as in pregnancy or in chronic pelvic inflammation; whereas they often retrogress during the temporary uterine involution of the puerperium and usually atrophy with the diminished blood supply of the menopause. It was also observed that occasionally myomas keep on growing after the menopause if they have an extrauterine blood supply by adhesions or by their atypical location.

Such observations have formerly led to the belief that the amount of blood supply was the basic factor controlling the growth of myoma.

In recent years it has been proved that the circulation of the uterus itself, and with it the circulation of the uterine myomas, is controlled to a great extent by hormonal action in synergism with the vegetative nervous system. It has been shown that estrin produces hyperemia of the uterus and that this circulatory trophic action is one phase of growth stimulation exerted by estrogen. The physiologic and pathologic conditions accompanied by hyperemia which seem to favor the growth of myoma are commonly associated with, or even partially produced by, increased or unbalanced estrogenic action.

A number of analogies are suggested when we compare experimental production of fibroids in guinea pigs with the spontaneous development of myoma in the human being. If we follow up these analogies and compare the sequence of experimental steps with the variety of factors thought responsible for the development of the human myoma, we may be enabled to fill in the gaps between various seemingly unconnected factors involved in the genesis of myoma. Some of these analogies seem to fit in readily with certain known clinical facts.

For example, corresponding to the production of experimental fibroids, it seems plausible that human myomas are more likely to be produced

TABLE I. CLINICAL OBSERVATIONS

| PATIENT                | NO. MG. GIVEN | DOSAGE  | RESULT   |
|------------------------|---------------|---|--|
| Vitamin B <sub>1</sub> |               |   |  |
| D. B.                  | 150           | Three 50 mg. injections over a period of 1 week               | Complete relief of nausea                                  |
| W. B.                  | 620           | 25 to 50 mg. injections over period of 2 to 7 days            | Nausea and vomiting  |
| H. C.                  | 100           | Two 50 mg. injections over period of one month                | Relief the first month. Repeated second. No recurrence     |
| H. C.                  | 350           | 50 and 100 mg. doses at week intervals                        | Usually relieved in about four days                        |
| J. D.                  | 100           | 1 dose  | Vomiting cleared. Nausea not marked thereafter             |
| E. D.                  | 200           | Two 50 mg. injections at two-day intervals                    | Relief for 48 hours  |
|                        |               | Four 25 mg. injections at six-day intervals                   | No vomiting. Nausea relieved in four days                  |
| J. D.                  | 50            | 1 dose  | Immediate relief   |
| M. D.                  | 250           | Ten 25 mg. injections intravenously                           | Temporary relief after each dose for three or four days    |
| H. D.                  | 100           | Four 25 mg. injections  | Nausea and vomiting relieved in three or four days         |
| M. E.                  | 100           | Four 25 mg. injections at week intervals                      | Greatly improved in three days                             |
| C. E.                  | 25            | 1 dose intravenously  | Marked improvement   |
| W. F.                  | 150           | Three 50 mg. injections                                       | Vomiting ceased  |
| J. F.                  | 50            | 1 dose intramuscularly  | Relieved entirely  |
| L. F.                  | 250           | One 100 mg. injection   | Relieved. Nausea returned in two weeks                     |
|                        |               | 25 and 50 mg. injections                                      | Relief for a week after each injection                     |
| E. G.                  | 100           | 50 mg. injections at two-week intervals                       | Relieved   |
| L. J.                  | 25            | 1 dose  | Complete relief  |
| L. G.                  | 250           | Five 50 mg. injections intramuscularly from 4 to 5 days apart | Relieved after each injection                              |
| S. H.                  | 150           | Two 50 mg. injections<br>Two 25 mg. injections                | No relief  |
| T. H.                  | 100           | Two 50 mg. injections over period of 8 days                   | Relieved entirely after second dose                        |
| P. I.                  | 200           | One 100 mg. injection<br>Two 50 mg. injections                | Improved but not completely<br>Relieved vomiting           |
| G. J.                  | 300           | Three 100 mg. injections at wide intervals                    | Coincided periods of depression. Moderate temporary relief |
| B. K.                  | 125           | 25 and 50 mg. injections at week intervals                    | Good results. Last dose given for fatigue                  |

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## CLINICAL OBSERVATIONS IN TREATMENT OF NAUSEA AND VOMITING IN PREGNANCY WITH VITAMINS B<sub>1</sub> AND B<sub>6</sub>

### A PRELIMINARY REPORT

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**P**ERNICIOUS vomiting of pregnancy has long been a nemesis to the physician practicing obstetrics as well as to the unfortunate patient. Relief has often been obtained from liver injections as well as from hospitalization with attendant intravenous glucose infusions, a method often having the disadvantage of being both slow and expensive. Vitamin B<sub>1</sub> has more recently been introduced into this field with some success; but here again the persistent case of hyperemesis gravidarum has not responded with entire satisfaction.

Herewith is reported an experience with the use of vitamin B<sub>6</sub> in what is believed to be a new therapy for this condition. This treatment is recommended, because it seems more effective and is simpler to administer.

In May, 1941, vitamin B<sub>6</sub> was administered to an obstetric patient, Mrs. M. Mrs. M. had intelligently cooperated in every trial of a remedy and had completely failed to respond to any treatment. Since she had been similarly incapacitated with her first pregnancy, she concurred in a desire to try the results of vitamin B<sub>6</sub>. An intravenous injection of 2 c.c. (20 mg.) was made and the patient was told to report results. Four days later she returned with the story of having been able to retain her evening meal on the day of the injection, and



TABLE I—CONT'D

| PATIENT                | NO. MG. GIVEN | DOSAGE  | RESULT                                       |
|------------------------|---------------|---|--|
| Vitamin B <sub>6</sub> |               |   |  |
| C.                     | 1000          | Twenty 50 mg. injections  | Vomits occasionally                          |
| R.                     | 1250          | Twenty-five 50 mg. injections   | Vomits some but not confined to bed          |
| S.                     | 1500          | Thirty 50 mg. injections given tri-weekly for 3 weeks. Discontinued and vomiting returned. Began again tri-weekly | Was well as long as B <sub>6</sub> was given |
| L.                     | 750           | Fifteen 50 mg. injections   | Much improved                                |
| H.                     | 500           | Ten 50 mg. injections   | Improvement                                  |
| P.                     | 150           | Three 50 mg. injections   | Relieved                                     |
| T.                     | 150           | Three 50 mg. injections   | Much improved                                |
| B. K.                  | 100           | Two 50 mg. injections intravenously on successive days  | Excellent results                            |
| R. H.                  | 100           | Two 50 mg. injections intravenously 5 days apart  | Good results                                 |
| R. B.                  | 250           | Five 50 mg. injections intravenously from one- to five-day intervals  | 75% improvement                              |
| G. R.                  | 400           | Eight 50 mg. injections intravenously from 1 to 5 days apart  | 75% improvement                              |
| L. K.                  | 100           | Two 50 mg. injections intravenously on successive days  | Complete relief                              |
| W. J.                  | 100           | Two 50 mg. injections intravenously 1 day apart   | Excellent results                            |
| R. E.                  | 150           | Three 50 mg. injections on successive days. Given intravenously   | Excellent results                            |
| J. McC.                | 200           | Four 50 mg. injections intravenously on successive days   | About 50% improvement by fourth dose         |
| D. D.                  | 250           | Five 50 mg. injections  | Relief from vomiting. Slight nausea          |
| H. C.                  | 125           | Three injections given from two- to five-day intervals  | Excellent results                            |
| D. H.                  | 450           | Nine 50 mg. injections twice weekly   | Good results                                 |
| S. D.                  | 250           | Five 50 mg. injections twice weekly   | Excellent results                            |
| D. F.                  | 100           | Two 50 mg. injections one week apart  | Improvement                                  |
| S. G.                  | 200           | Four 50 mg. injections twice weekly   | Complete relief                              |
| R. H.                  | 400           | Eight 50 mg. injections intravenously tri-weekly  | Excellent results                            |

TABLE I—CONT'D

| PATIENT | NO. MG. GIVEN | DOSAGE   | RESULT   |
|---------|---------------|--|--|
| J. L.   | 275           | 25 mg. injections at one-week intervals                            | Temporary four-day relief  |
| W. L.   | 600           | 25 mg. injections  | No relief given account limited diet to keep up concentration B <sub>1</sub> . Weight kept up fairly well, ceased after 2 units crude liver given. One 300 c.c. blood transfusion for proteins |
| W. M.   | 25            | 1 dose intravenously   | Relief   |
| R. M.   | 150           | Three 50 mg. injections  | Acute cold after taking  |
| G. M.   | 200           | One 100 mg. injection<br>Two 50 mg. injections 1 day interval      | Neuritis in arm and nausea<br>Moderate relief of nausea  |
| M. N.   | 50            | Two 25 mg. doses   | Immediate relief after each dose. No further injections needed   |
| R. P.   | 75            | 25 and 50 mg. doses  | Relief marked but not complete   |
| J. R.   | 275           | 25 and 50 mg. injections given at three-day intervals, then weekly | Vomiting ceased  |
| D. R.   | 900           | 25 and 50 mg. injections every 3 or 4 days                         | Became nauseated if discontinued   |
| G. S.   | 50            | 1 injection  | Relief from vomiting. Moderate nausea  |
| B. S.   | 300           | Six 50 mg. injections  | Relief for 5 or 6 days   |
| L. S.   | 25            | 1 dose intravenously   | No result  |
| N. S.   | 250           | Five 50 mg. injections given every 4 days                          | Vomiting ceased and nausea moderated   |
| S. S.   | 75            | 25 and 50 mg. doses  | Improved   |
| N. S.   | 825           | 25 and 50 mg. doses given every 2 or 3 days                        | Temporary relief for 1 to 2 days. Nausea returned if discontinued injections   |
| S. S.   | 125           | One 100 and one 25 mg. injection                                   | Improved after first injection   |
| J. S.   | 100           | 1 injection  | Improved   |
| N. T.   | 100           | Two 50 mg. injections  | No improvement   |
| L. W.   | 350           | Seven 50 mg. injections at weekly intervals                        | Temporary relief of nausea after each injection  |
| H. W.   | 25            | 1 dose intravenously   | No improvement   |
| E. W.   | 100           | Two 50 mg. doses one week apart                                    | Relieved nausea and severe vomiting  |
| R. W.   | 600           | 10 mg. daily intravenously over a period of 2 months               | Immediate improvement with recurrence when discontinued  |

cluded, vitamin B<sub>6</sub> is the most efficient therapeutic agent in nausea and vomiting of pregnancy so far tried. It has the added advantage of being practical for office use as well as economical.

Results of these treatments were passed on to the Obstetrical Staff at Baylor University College of Medicine. To date, vitamins B<sub>1</sub> and B<sub>6</sub> have been administered by different members of the Staff. A report of the clinical observations was made to the regular monthly staff meeting of Baylor Hospital on Jan. 22, 1942.

It has been repeatedly observed that the deliberate ingestion of food materially lessens the early nausea and vomiting in pregnancy. With this thought in mind, we have attempted to create a desire for food by the administration of vitamin B<sub>1</sub> or B<sub>6</sub> to all patients who complained of any degree of nausea and vomiting in the first trimester of pregnancy.

George R. Cowgill (*Am. J. Physiol.* 57: 1921) published a paper, "A Contribution to the Study of the Relation Between Vitamin B and the Nutrition of the Dog." Itemizing experiments on the hunger of dogs and verifying a report published by Karr in 1920, he drew this conclusion: "The observation of Karr, 'that some relationship exists in the dog between the desire to partake of food and the amount of the so-called water-soluble vitamine ingested,' has been confirmed." To the list of substances reported by Karr, Cowgill added alcoholic extracts of wheat embryo, rice polishings, and navy bean, and made the following statement: "All of the products were tested and found to restore appetite or to relieve polyneuritic symptoms."

Again, Cowgill and co-workers (*Am. J. Physiol.* 77: 1926) on the subject, "Studies in the Physiology of Vitamins," published an article on "Vitamin B in Relation to Gastric Motility." Among the conclusions of this paper he states: "It is difficult to decide whether or not vitamin B maintains the desire to eat simply by aiding in the preservation of the normal gastric tone. The marked systemic manifestations characteristic of advanced cases of vitamin B deficiency suggest that the loss of the desire to eat in such cases is due as much to a generalized systemic disturbance as it is to an abnormal condition localized in the alimentary canal."

Further, in October, 1937, Dr. Charles Martin, Professor of Radiology, Baylor University College of Medicine, in a preliminary report on "The Treatment of Roentgen Sickness With Synthetic Vitamin B<sub>1</sub> Hydrochloride," states in his conclusions: "Vitamin B<sub>1</sub> is an effective drug for the treatment of roentgen sickness. It is harmless and produces no complicating symptoms."

Since roentgen sickness is many times characterized by extreme nausea and pronounced vomiting similar to the nausea and vomiting of pregnancy, we began to administer first vitamin B<sub>1</sub> and later vitamin B<sub>6</sub> as a therapeutic measure for these symptoms in pregnancy.

#### SUMMARY AND CONCLUSIONS

1. Almost complete relief from nausea and vomiting of pregnancy was gained by administering vitamins B<sub>1</sub> and B<sub>6</sub> in a varying dosage

TABLE I—CONT'D

| PATIENT                     | NO. MG. GIVEN            | DOSAGE   | RESULT   |
|-----------------------------|--------------------------|--|--|
| H. H.                       | 300                      | Six 50 mg. injections three days apart           | Complete relief of vomiting. No nausea after last injection  |
| L. S.                       | 150                      | Three 50 mg. injections                          | No improvement   |
| J. M.                       | 100                      | Two 50 mg. injections                            | Good results   |
| J. N.                       | 200                      | Four 50 mg. injections intravenously             | Excellent results  |
| R. S.                       | 150                      | Three 50 mg. injections                          | Complete relief  |
| F. S.                       | 250                      | Two 50 mg. injections intramuscularly            | No relief  |
|                             |                          | Three 50 mg. injections intravenously            | Partial relief   |
| R. P.                       | 300                      | Six 50 mg. injections intravenously 2 days apart | Relief after second injection  |
| M. A.<br>(10 wk. gestation) | 150                      | Three 50 mg. injections                          | Complete relief of vomiting. No nausea for 3 days after each injection. Able to continue office work   |
| A. K.                       | 300                      | Six 50 mg. injections                            | Partial relief after first dose. No nausea after last injection  |
| G. S.                       | 50                       | One 50 mg. injection                             | Improved   |
| R. G.                       | 250<br>(B <sub>6</sub> ) | 50 mg. injections intravenously daily            | No improvement whatsoever  |
|                             | 375<br>(B <sub>1</sub> ) | 50 mg. injections intravenously daily            | No improvement. Nausea, vomiting, and ptialism continued   |
| H. B.                       | 150                      | Three 50 mg. injections                          | Relief from slight nausea. Patient had complained bitterly of a migraine. <i>Migraine was relieved</i> |
| J. S.                       | 50                       | One 50 mg. injection                             | Patient had no nausea but had a migraine for 2 weeks. Migraine relieved for 48 hours after injection   |
| C. B.                       | 50                       | One 50 mg. injection                             | Complete relief  |
| R. P.                       | 50                       | One 50 mg. injection                             | Relief of vomiting. Slight nausea  |

of having been almost entirely free of nausea until the fourth day. She came in to ask for another dose. The injections were repeated until five doses were administered. Following these injections, she had no return of nausea or vomiting.

This experiment led to the use of similar treatment for Mrs. McM., a patient of the same type. She responded as quickly and as completely as the first case. Thereafter this vitamin was made a routine treatment in cases of vomiting of pregnancy. Apparently, it was con-

TABLE I

| CASE     | STAGE<br>OF PREG-<br>NANCY<br>IN<br>WEEKS | SYMPTOMS                                 |                                   | PREVIOUS<br>OBSTETRIC<br>HISTORY*  | BLOOD<br>ESTRIN <sup>4</sup> * | THERAPY*<br>(DAILY)                   | RESULTS                                  |
|----------|---|--|-----------------------------------|--|--------------------------------|---------------------------------------|--|
|          |   | PAINS                                    | BLEED-<br>ING                     |  |                                |                                       |  |
| 1        | 31  | +  | 0                                 | 1 term child<br>after toxemic<br>pregnancy;<br>one normal<br>term preg-<br>nancy | Neg. at<br>30 weeks            | 0                                     | 8 lb. normal<br>term boy                 |
|          | 37  | +  | +(spots)                          |  |                                | 3ii w.g.o.                            |  |
| 2        | 28  | +(labor<br>pains)                        | 0                                 | 0  | Neg. at<br>28 weeks            | 3iv w.g.o.                            | 5½ lb. prema-<br>ture normal<br>girl     |
|          | 34  | +  |                                   |  |                                | Off w.g.o.<br>for 4<br>days<br>before |  |
| 3        | 32  | +  | +(spots)                          | Stillborn (tox-<br>emic) at term   | Pos. at<br>8 weeks             | 3ii w.g.o.                            |  |
|          | 33  | +  | +(spots)                          |  |                                | Exam.<br>shows no<br>previa           |  |
|          | 34  | +  | +(mod-<br>erate<br>bleed-<br>ing) | 0  |                                |                                       |  |
|          | 37  | 0  | +(spots)                          |  |                                |                                       |  |
|          | 38  | 0  | +(spots)                          |  |                                |                                       |  |
| 3<br>(a) | 32  | +  | 0                                 | 1 term still-<br>born, 1 nor-<br>mal term child                                  | Pos. at<br>6 weeks             | 3iv w.g.o.                            | 7 lb. 4 oz. nor-<br>mal term boy         |
| 4        | 28  | +  | 0                                 | 1 spont. ab.;<br>many threats<br>this pregnancy                                  | Pos. at<br>5 weeks             | 3ii w.g.o.<br>and bed                 | 5 lb. normal<br>premature girl           |
|          | 32<br>34                                  | +(<br>Spont.<br>rupt.<br>mem-<br>branes) | 0<br>0                            |  |                                |                                       |  |
| 5        | 28  | +  | 0                                 | 1 toxic preg-<br>nancy with<br>normal term<br>child                              | Pos. at<br>13 weeks            | 3i w.g.o.                             | Normal term<br>child                     |
|          | 32  | +(labor<br>pains<br>for 12<br>hours)     | 0                                 |  |                                |                                       |  |
|          | 34  | 0  | +(mod.)                           |  |                                |                                       |  |
|          | 36  | 0  | +(spots)                          |  |                                |                                       |  |
| 6        | 37  | +(spont.<br>rupt.<br>mem-<br>branes)     | 0                                 | 0  | Pos. at<br>24 weeks            | 3i w.g.o.                             | 5 lb. 7 oz. nor-<br>mal premature<br>boy |

\*w.g.o., wheat germ oil; pos., positive; neg., negative; spont. ab., spontaneous abortion.

at irregular intervals and by either the intramuscular or intravenous route.

2. Relief from nausea and vomiting occurred more often and more completely with the use of vitamin B<sub>6</sub> than with vitamin B<sub>1</sub>.

3. Many patients returned for injections only when nausea and vomiting reappeared.

4. No undesirable reactions were noted.

5. Two patients were relieved of an accompanying migraine.

6. This vitamin should be investigated as to its effect on vomiting due to other drugs, such as morphine, sulfanilamide, etc.

1529 MEDICAL ARTS BUILDING

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## VITAMIN E AND PREMATURE LABOR

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### INTRODUCTION

PREMATURITY per se is recognized as the greatest single cause of stillbirths and neonatal deaths. There is no need to cite the actual statistics on this enormous wastage of infant life. Moreover, a peculiar sterility pervades medical papers dealing with its prophylaxis. Such clichés as "better prenatal and pediatric care," "adequate rest" and "a nourishing diet" appear in them all too frequently—remarks which are singularly unhelpful and imply a too casual approach to the study of this situation. Baird and Wyper<sup>1</sup> point out: "Among booked cases only slight improvement in the infant death-rate can be looked for by improvement in treatment along the present lines. The big factors are the toxemias—unexplained premature labor, and unexplained death."

It was suggested in 1937<sup>2</sup> that premature labor might be due to the same pathologic endocrine background responsible for spontaneous abortion and that vitamin E should be as valuable in the prevention of premature delivery as in the prevention of abortion.

Kotz, Parker and Kaufman<sup>3</sup> also have concluded that probably the same factors causing bleeding in early pregnancy are responsible for the onset of premature labor, and that the etiology of the latter is, therefore, to be sought in the endocrine constitution of the mother. They gave their patients of this type a combination of vitamin E, thyroid extract, and progesterone until term.

I desire to present here a detailed report of my results in private practice when using only vitamin E for 46 threatened premature deliveries.

TABLE I—CONT'D

| CASE | STAGE<br>OF PREG-<br>NANCY<br>IN<br>WEEKS | SYMPTOMS   |                                    | PREVIOUS<br>OBSTETRIC<br>HISTORY*                       | BLOOD<br>ESTRIN <sup>4</sup> * | THERAPY*<br>(DAILY)  | RESULTS   |
|------|---|--|------------------------------------|---|--------------------------------|--|---|
|      |   | PAINS  | BLEED-<br>ING                      |   |                                |  |   |
| 16   | 32  | +  | 0                                  | 2 normal term children                                  | Neg. at 17 weeks               | 3i w.g.o.  | 9 lb. 7 oz. term boy with bad cleft palate, harelip and bloody amniotic fluid                   |
|      | 33  | +  | 0                                  |   |                                | 3iv w.g.o.   |   |
| 17   | 29  | +  | 0                                  | 0   | Neg. at 8 weeks                | 3vi w.g.o.   | 7 lb. 6 oz. normal term boy   |
|      | 36  | +<br>(labor pains for 6 hr. after husband lost overseas) |                                    |   |                                |  |   |
| 18   | 32  | +  | +<br>(moderate)                    | 0   | Pos. at 3 weeks                | 3lss w.g.o.  | 6 lb. 6 oz. normal term girl  |
| 19   | 28  | 0  | +<br>(moderate for 3 days)         | 1 term child and 1 spont. ab. Many bleedings this preg. | Not done                       | 3lss w.g.o.  | 8 lb. 4 oz. normal term boy   |
| 20   | 29  | +  | 0                                  | 2 normal children                                       | Pos. at 5 weeks                | 3vi w.g.o.   | 7 lb. 4 oz. term girl. It died at 2½ mo. after operation revealed complete absence of bile duct |
|      | 31  | +  | 0                                  |   |                                | 3i w.g.o. and bed  |   |
| 21   | 36  | +<br>(active)  | +<br>(moderate for 6 days)         | 0   | Pos. at 27 weeks               | 3i w.g.o.  | 7 lb. normal term child   |
| 22   | 28  | 0  | +<br>(spots)                       | 0   | Pos. at 24 weeks               | 3ii w.g.o.   | Stillborn normal breech at 36 weeks   |
|      | 31  | 0  | +<br>(spots every day for 2 weeks) |   |                                | 3iv w.g.o.   |   |
|      | 32  | 0  | Mod-<br>erate bleed-<br>ing        |   |                                | Exam. for previa neg. so 3i w.g.o. begun. Bad pyelitis developed |   |

TABLE I—CONT'D

| CASE      | STAGE<br>OF PREG-<br>NANCY<br>IN<br>WEEKS | SYMPTOMS  |  | PREVIOUS<br>OBSTETRIC<br>HISTORY*   | BLOOD<br>ESTRIN <sup>4</sup> * | THERAPY*<br>(DAILY) | RESULTS   |
|-----------|---|---|--|---|--------------------------------|---------------------|---|
|           |   | PAINS   | BLEED-<br>ING                          |   |                                |                     |   |
| 7         | 34  | 0   | 0                                      | 1 spont. ab.,<br>many threats<br>this preg.                                     | Pos. at<br>28 weeks            | 6 mg.<br>ephynal    | 7½ months<br>macerated<br>fetus delivered<br>by induction |
| 8         | 34  | 0   | +<br>(spots)                           | 1 normal term<br>child (tox-<br>emic after<br>sixth month)                      | Pos. at<br>26 weeks            | 3ii w.g.o.          | 8 lb. normal<br>term girl                                 |
| 9         | 28  | +   | +<br>(brisk)                           | 1 term child<br>and 1 term<br>mongolian   | Pos. at<br>10 weeks            | 3iv w.g.o.          | Normal prema-<br>ture, lived 4<br>hours                   |
| 10        | 34  | +   | 0                                      | 2 term children<br>with toxemia<br>first preg. and<br>threatened ab.<br>in both | Pos. at<br>12 weeks            | 36 mg.<br>ephynal   | 10 lb. normal<br>term boy                                 |
| 11        | 34  | +<br>(labor<br>pains<br>4 hr.)                  | 0                                      | 1 normal preg-<br>nancy   | Neg. at<br>7 weeks             | 3ii w.g.o.          | 8 lb. normal<br>term child                                |
| 12        | 34  | +<br>(to hosp.<br>ready<br>for deliv-<br>ery)   | 0                                      | 0   | Pos. at<br>34 weeks            | 3iv w.g.o.          | 7 lb. 6 oz. nor-<br>mal term child                        |
| 13        | 28  | +<br>(se-<br>vere)                              | +<br>(spots<br>nearly<br>every<br>day) | 0   | Pos. at<br>10 weeks            | 3iv w.g.o.          |   |
|           | 32  | +   | +<br>(spots)                           |   |                                |                     | 7 lb. 6 oz. nor-<br>mal term child                        |
| 14        | 34  | +   | 0                                      | 1 normal term<br>child  | Pos. at<br>11 weeks            | 3i w.g.o.           | 6 lb. 6 oz. nor-<br>mal boy                               |
| 15        | 35  | +   | 0                                      | 1 term child<br>with harelip<br>and cleft<br>palate                             | Pos. at<br>9 weeks             | 3ii w.g.o.          |   |
|           | 38  | +<br>(crying<br>with<br>pains)                  | 0                                      |   |                                |                     | 7 lb. normal<br>term girl                                 |
| 15<br>(a) | 33  | +   | 0                                      | 1 deformed and<br>one normal<br>child   | Neg. at<br>3 weeks             | 3vi w.g.o.          | 7 lb. normal<br>term boy                                  |
| 15<br>(b) | 32  | +   | 0                                      | 1 deformed and<br>two normal<br>children  | Not done                       | 3i w.g.o.           |   |
|           | 36  | +<br>(labor<br>pains<br>nearly<br>every<br>day) | 0                                      |   |                                |                     | 6 lb. 4 oz. nor-<br>mal term boy                          |



TABLE I—CONT'D

| CASE | STAGE<br>OF PREG-<br>NANCY<br>IN<br>WEEKS | SYMPTOMS                             |                                   | PREVIOUS<br>OBSTETRIC<br>HISTORY*   | BLOOD<br>ESTRIN <sup>4</sup> * | THERAPY*<br>(DAILY)  | RESULTS  |
|------|---|--------------------------------------|-----------------------------------|---|--------------------------------|--|--|
|      |   | PAINS                                | BLEED-<br>ING                     |   |                                |  |  |
| 33   | 30  | 0                                    | +<br>(brisk bleed-<br>ing)        | 2 normal term<br>children   | Pos. at<br>26 weeks            | 3i w.g.o.  | 7 lb. normal<br>term girl.<br>Placenta im-<br>mediately<br>after baby          |
| 34   | 36<br>38                                  | +<br>typical<br>labor<br>pains       | 0<br>0                            | 6½ months<br>spont. miscar-<br>riage  | Pos. at<br>10 weeks            | 3i w.g.o.<br>up to 30<br>mg.<br>ephynal  | 8 lb. normal<br>term boy   |
| 35   | 32<br>36                                  | +<br>(la-<br>bor<br>pains)           | 0<br>0                            | 1 toxic term<br>preg.   | Not done                       | 3i w.g.o.<br>9 mg.<br>ephynal<br>and 3iv<br>w.g.o.                             | 8 lb. normal<br>term boy   |
| 36   | 31  | +                                    | 0                                 | 5 weeks spont.<br>ab.   | Pos. at<br>4 weeks             | Ephynal<br>mg. 10<br>per day   | Macerated pre-<br>mature twins<br>at 7 months                                  |
| 37   | 28<br>36                                  | 0<br>+<br>(strong<br>labor<br>pains) | +<br>(spots)<br>0                 | 1 normal term<br>child  | Pos. at<br>4 weeks             | 30-50 mg.<br>of<br>ephynal<br>75-125 mg.<br>of<br>ephynal                      | Normal term 7<br>lb. 2 oz. boy<br>with typical<br>abruptio type<br>of placenta |
| 38   | 30<br>31<br>34                            | +<br>+<br>+                          | +<br>(spots)<br>0<br>+<br>(spots) | 1 eclampsia<br>(postpartum)<br>1 normal term<br>child<br>1 abortion<br>1 toxic preg.<br>at term | Not done                       | 3iv w.g.o.<br>3i w.g.o.<br>3iss w.g.o.   | 7 lb. normal<br>term child   |
| 39   | 28<br>34                                  | +<br>+                               | 0<br>0                            | 0   | Neg. at<br>3 weeks             | 3i w.g.o.<br>3i w.g.o.   | 7 lb. normal<br>term boy   |
| 40   | 31<br>33<br>34<br>38                      | +<br>+<br>+ (se-<br>vere)            | 0<br>+<br>(spots)<br>0<br>0       | 0   | Pos. at<br>12 weeks            | 30 mg.<br>ephynal<br>40 mg.<br>ephynal<br>50 mg.<br>ephynal<br>hence-<br>forth | 7 lb. 3 oz. nor-<br>mal term boy   |
| 41   | 35  | +                                    | 0                                 | 0   | Pos. at<br>19 weeks            | 3ii w.g.o.   | Premature 4<br>lb. 9 oz.<br>female (extro-<br>cardia), lived<br>one day        |

## DISCUSSION

It is whipping a straw horse to repeat<sup>5</sup> that premature expulsion of the fetus at any stage of pregnancy may be due to more than one single cause, viz., deficiency of vitamin E. But there are etiologic factors of

TABLE I—CONT'D

| CASE      | STAGE<br>OF PREG-<br>NANCY<br>IN<br>WEEKS | SYMPTOMS                                     |                            | PREVIOUS<br>OBSTETRIC<br>HISTORY*          | BLOOD<br>ESTRIN* <sup>4</sup>             | THERAPY*<br>(DAILY)  | RESULTS   |
|-----------|---|--|----------------------------|--|---|--|---|
|           |   | PAINS  | BLEED-<br>ING              |  |   |  |   |
| 23        | 31  | 0  | +<br>(spots)               | 1 spont. ab.                               | Pos. at<br>14 weeks                       | 3iv w.g.o.   | 7 lb. 10 oz. nor-<br>mal term boy   |
| 23<br>(a) | 34  | +  | 0                          | 1 spont. ab.<br>and 1 term<br>child        | Pos. at<br>8 weeks                        | 3ii w.g.o.   | 8 lb. normal<br>term girl   |
| 24        | 28  | Spont.<br>rupt.<br>mem-<br>branes            | 0                          | 1 spont. ab.<br>Many threats<br>this preg. | Not done                                  | 3i w.g.o.  | Anencephalus<br>with clubfeet<br>at 33 weeks  |
|           | 33  | +  | +<br>(brisk bleed-<br>ing) |  |   |  |   |
| 25        | 33<br>37                                  | +<br>+<br>strong                             | 0<br>0                     | 0  | Pos. at<br>8 weeks                        | 3iv w.g.o.   | 7 lb. 8 oz. nor-<br>mal term still-<br>born due to<br>prolapsed cord<br>in breech<br>presentation |
| 25<br>(a) | 31  | +  | 0                          | 1 term still-<br>birth                     | Neg. at<br>5 weeks                        | 3vi w.g.o.   | 8 lb. normal<br>term boy  |
| 26        | 32<br>36<br>37                            | +<br>+ (se-<br>vere)<br>+ (se-<br>vere)      | 0<br>0<br>0                | Ectopic and<br>one term<br>child           | Not done                                  | 3vi w.g.o.   | 7 lb. 8 oz. nor-<br>mal term girl   |
| 27        | 35  | +  | 0                          | 0  | Pos. at<br>4 weeks                        | 3i w.g.o.  | Macerated pre-<br>mature male<br>3 lb. 4 oz.  |
| 28        | 36  | 0  | +<br>(spots)               | 0  | Neg. at<br>18 weeks                       | 3ii w.g.o.   | 7 lb. normal<br>term girl   |
| 29        | 30  | +  | +<br>(spots)               | 0  | Pos. at<br>26 weeks                       | 3iv w.g.o.<br>Then extra<br>doses for<br>one day.<br>Rupt.<br>mem-<br>branes.<br>3iv w.g.o.<br>q.i.d. and<br>b.i.d.<br>After 3<br>days<br>went into<br>labor | Premature<br>twins of 2 lb.<br>12 oz. and 2<br>lb. 5 oz.<br>Lived 2-6<br>hours only               |
| 30        | 37  | 0  | +<br>(spots)               | 1 term sp.<br>bifida                       | Pos. at<br>14 weeks                       | Ephynal<br>mg. 30  | 8 lb. 8 oz. nor-<br>mal term boy  |
| 31        | 29<br>30                                  | +<br>to hos-<br>pital<br>for<br>"la-<br>bor" | 0                          | 1 term child                               | Pos. at<br>10 weeks                       | 3iv w.g.o.<br>up to<br>3viii<br>w.g.o.   | 9 lb. normal<br>term girl   |
| 32        | 38  | +  | +<br>(gush)                | 0  | Neg. at<br>4 weeks<br>Neg. at<br>18 weeks | 3i w.g.o.  | 8 lb. 8 oz. nor-<br>mal term boy  |

Twenty-seven of these 41 women had had one or more previous pregnancies. Sixty-one per cent of these 38 previous pregnancies had ended in toxemias, monstrosity, stillbirth, or in abortion or some such premature expulsion of the fetus. This falls in line with Young's conception of the "abortion sequence."<sup>11</sup> If the patient is able to avoid the Scylla of abortion or miscarriage she exposes herself to the Charybdis of prematurity, toxemia, or monstrosity. This sequence of dangers can be suspected before pregnancy if she is a hypothyroid and in the earliest weeks of pregnancy if she has an elevated blood estrogen level. Many scores of times the estrogen assay has foretold trouble months before it was detectable clinically.

The dose of vitamin E required to preserve a precarious pregnancy in "normal" condition rises gradually toward term, which could be inferred from the fact that E insures proper placentation;<sup>12</sup> more should be needed as the placenta enlarges. It is not surprising, therefore, that very large doses of wheat germ oil or synthetic alphatocopherol acetate were needed to prevent premature delivery in many of the women cited in the table.

The wisdom of attempting to preserve these unsettled pregnancies has often been questioned. The writer has repeatedly<sup>13-15</sup> urged that it was worth while, and Falls<sup>16</sup> has recently supported this view. Certainly, only 3 of the 41 live children secured in this series were defectives (7 per cent). The anomalies delivered were a cleft palate and hairlip, a congenital bile duct obliteration, an anencephalus with clubfeet, and an extrocardia, but only one of these could and did live as long as three months. One must weigh his misfortune against the potential value of the lives of the other 38 children preserved either by Nature or vitamin E or both. The choice before the attending obstetrician, as seen in this light, seems obvious.

Doubtless some of these threats of premature delivery would have subsided without any treatment. But I have watched every one of these anxiously and carefully and am inclined to ascribe their outcome more to vitamin E than fate. The series is uncontrolled, but obstetricians have been watching untreated series of these cases for too many decades. The poor results of expectant treatment are only too well known.

#### SUMMARY

1. A series of 46 cases of threatened premature labor is presented. A blood test for imbalance between estrogens and vitamin E was done on 40 of these pregnant women when first seen. Seventy-three per cent revealed estrogen excess.

2. All were treated prophylactically, or at the time of the threat, with vitamin E. Where E is indicated in any precarious pregnancy, it should be given in gradually increasing dosage until term.

the first importance and many of very minor significance; disturbance of the estrogen: vitamin E equilibrium<sup>6</sup> appears to be the most important of the primary causes. This is illustrated by the fact that estrogen excess was discovered very early in 73 per cent of the 40 of these 46 pregnancies tested for it and also by the success of vitamin E in preserving so many of these precarious gestations. It is felt very strongly that even more of these pregnancies could have been preserved had larger doses of vitamin E been used prophylactically. Our results have improved greatly as we have moved in this direction.

Many women experience several threats to the integrity of a pregnancy between its beginning and term. It is probably safe to assume that much the same cause is operative each time. It is important, therefore, that the status of each pregnant woman should be studied as early as possible and that if such a prophylactic measure as the administration of vitamin E is indicated, it should be instituted at once. It is just as important, but more often overlooked, that E-therapy should be maintained until delivery at term. It should no longer be necessary to insist that only potent preparations of vitamin E should be used, the best being a fresh refrigerated bulk wheat germ oil or a synthetic alpha-tocopherol. Many of the products on the market are so unsatisfactory that it is no wonder that E-therapy lies under a cloud at the moment.

Sometimes the first clinical inkling of premature delivery, however, is a sudden rupture of the membranes. This almost inevitably spells labor, although we have seen pregnancy continue for weeks and months thereafter in four women (one being Case 24) to whom this happened and who were promptly given huge doses of vitamin E. It is desirable, therefore, that such a danger should be foreseen, if possible; for that reason, I test the blood estrin<sup>4</sup> of each pregnant woman at her first antenatal visit. The table illustrates in part how useful this test has proved. It has been seriously criticized,<sup>7, 8</sup> although something has been said in its defense<sup>9, 10</sup> too. Its clinical utility in our hands is beyond doubt. For example, 73 per cent of the patients tested revealed estrogen excess and 76 per cent were taken to term with the delivery of living children after the administration of vitamin E. These figures are scarcely a coincidence. It is suggested that either it or an alternative method of assay is a *sine qua non* in the prophylaxis of prematurity.

Much more bleeding can occur in late than in early pregnancy without unduly jeopardizing its integrity. Probably this is due to the greater proportion of adequately adherent placenta that remains undisturbed in the former. It could be anticipated, therefore, that late pregnancies would be more easily preserved than early ones, and that is our experience.

both children premature by definition. The 861 infants were therefore born to 827 mothers. The mothers of 347 children were primigravidas (40.3 per cent). All but 18 of the women were white. The majority of the patients were indigent (783), married (702), and adherents to the protestant religions (626). Forty-one women were syphilitic (5.0 per cent).

During the years 1926 to 1935, the premature children were housed in the regular nursery where there was one old-model incubator. Thermostatic regulation served to keep the temperature between 75° and 80° F., while heat cradles were available to supplement the single incubator. No attention was paid to the humidity of the air. Fresh breast milk was frequently available from ward patients. An isolation nursery was in use. During the last six years covered by the report, all children under 2,500 Gm. in weight were cared for in a special nursery without cubicles. The temperature was hand regulated and an attempt was made to keep the room at 85° F. A relative humidity of approximately 50 per cent was maintained by a simple, hot-water spray humidifier. Frozen breast milk was available to supplement that obtained directly from nursing women. Gauze masks were worn by all attendants from 1930 to 1935, inclusive, but not during the other intervals. During the entire 15 years the nurseries were under the control of the obstetric staff but excellent pediatric consultation was always available and was frequently requested.

*Fetal and Infant Mortality.*—There were 165 (19.2 per cent) stillbirths and 153 (17.7 per cent) infants who died before discharge from the hospital, leaving 543 (63.1 per cent), who were dismissed alive. Through the assistance of the Division of Vital Statistics of the Iowa State Department of Health, it was learned that at least 36 of those discharged alive died before the end of the first year. This postneonatal mortality rate (66 per 1000) is higher than would have been expected among an equal number of term children. The total salvage at the end of twelve months was approximately 58.9 per cent, whereas 70.5 per cent of the prematures from twin births survived. The greatest neonatal mortality was during the first day when 108 (71.4 per cent) of the 153 deaths occurred. Only 21 died after the first week, exclusive of those who died after the first month.

In the five and one-half years after the introduction of air humidifiers in the nursery (1936 to 1941), there were 447 prematurely born children with 297 survivors (66.4 per cent), in contrast to the 414 born in the preceding nine and one-half years with 246 survivors (59.3 per cent).

Masking was in vogue for six years (1930 to 1935, inclusive) during which there were 347 premature infants with 207 survivors (59.1 per cent), as compared with 514 and 336 survivors (65.3 per cent) in the other nine years when masks were not worn. Upon comparing the earlier period (1926 to 1929) when there was no masking and no humidification and the most recent period (1936 to 1941) when masking was not employed but humidity control was exercised, the mortality rates are 53.3 and 66.4 per cent, respectively.

3. Seventy-six per cent of the 46 patients were taken to term with the delivery of live children.

4. Seven per cent of the 41 live children delivered were defectives, but only one of these could and did live three months or longer.

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## MORTALITY OF PREMATURELY BORN INFANTS

## INFLUENCE OF CERTAIN ANTENATAL AND POSTNATAL FACTORS

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THE mortality rate of prematurely born infants is many times as great as that for full-term children. The chief factor which leads to this inordinate fatality is the imperfect development of the small baby and its inability to cope successfully with an extrauterine environment. Any attack upon the problem must consider not only the actual care of the premature infant but also the maternal or other factors which induced or necessitated the early termination of pregnancy. This study was undertaken to explore some of these factors as they appear in the children born in a state-operated general hospital catering largely (95 per cent) to the indigent population of an essentially rural district.

Any child weighing less than 2,500 Gm. at birth was considered prematurely born, irrespective of other anthropometric data or of the maternal menstrual history. Between July 1, 1926, and June 30, 1941, 861 infants weighing from 700\* to 2,499 Gm., among 14,594 born to 14,437 women, were included in this category, a prematurity incidence of 5.9 per cent. There were 27 pairs of twins with one child and 34 with

\*700 Gm. was selected as the lower level because no children weighing less and born alive in this Clinic have survived.

TABLE III. INFANT MORTALITY IN RELATION TO THE COMPLICATIONS OF PREGNANCY AND/OR LABOR

| COMPLICATIONS                           | TOTAL<br>NO. OF<br>CASES | FETAL SALVAGE   |             | STILLBIRTHS     |             | INFANT DEATHS<br>UNDER<br>ONE MONTH |             |
|---|--------------------------|-----------------|-------------|-----------------|-------------|-------------------------------------|-------------|
|   |                          | NO. OF<br>CASES | PER<br>CENT | NO. OF<br>CASES | PER<br>CENT | NO. OF<br>CASES                     | PER<br>CENT |
| Toxemia, nonconvulsive                  | 224                      | 120             | 53.6        | 69              | 30.8        | 35                                  | 15.6        |
| Eclampsia                               | 11                       | 4               | 36.4        | 6               | 54.5        | 1                                   | 9.1         |
| Placenta previa                         | 27                       | 7               | 25.9        | 14              | 51.8        | 6                                   | 22.3        |
| Prolapsed cord                          | 12                       | 1               | 8.3         | 11              | 91.7        | 0                                   | 0.0         |
| Premature separation of<br>the placenta | 10                       | 0               | 0.0         | 9               | 90.0        | 1                                   | 10.0        |
| Diabetes mellitus                       | 4                        | 1               | 25.0        | 3               | 75.0        | 0                                   | 0.0         |
| Intra-partum infection                  | 9                        | 4               | 44.4        | 5               | 55.6        | 0                                   | 0.0         |
| No complications                        | 598                      | 415             | 69.3        | 72              | 12.1        | 111                                 | 18.4        |

Intra-partum fever followed the induction of labor by Voorhees bag (2) and by premature rupture of the membranes (4), and also occurred after spontaneous onset (3).

TABLE IV. RELATION OF METHOD OF DELIVERY TO FETAL MORTALITY

| METHOD OF DELIVERY     | TOTAL CASES | MORTALITY    |          |
|------------------------|-------------|--------------|----------|
|                        |             | NO. OF CASES | PER CENT |
| Spontaneous            | 631         | 213          | 33.8     |
| Breech                 | 79          | 29           | 36.7     |
| Low forceps            | 56          | 17           | 30.4     |
| Version and extraction | 38          | 24           | 63.2     |
| Cesarean section       | 21          | 11           | 52.4     |
| Therapeutic abortion   | 12          | 12           | 100.0    |
| Midforceps             | 4           | 1            | 25.0     |
| No data                | 20          | 11           | 55.0     |
| Totals                 | 861         | 318          | 36.9     |

One hundred and twenty-three out of 142 previable babies (under 1,500 Gm.) died in comparison to 195 among 619 prematures (1,500 to 2,499 Gm.).

*Type of Delivery.*—The relation between the method of delivery and the fetal and infant mortality rates is shown in Table IV. The high death rates after version and extraction and therapeutic abortion may be explained by the relatively high incidence of children weighing under 1,500 Gm. In the entire series there were 142 previable infants with only 19 (13.4 per cent) survivors. In forceps deliveries and in breech extractions, the babies were generally larger and thus withstood the trauma of birth more satisfactorily.

The fact that there were 20 cesarean sections (21 infants) with such a high fetal and infant death rate deserves some attention. All of these operations were performed prior to July, 1938, and except in one instance, sterilization was carried out at the same time. There were 12 cases (two patients had a coincidental toxemia) where previous cesarean section was the primary indication for the procedure and where the time of operation was set by the premature onset of uterine contractions. The other 8 cases included 2 patients with chronic cardiac disease, 3 with severe hypertensive vascular disease, and one each with carcinoma of the cervix, dystocia following uterine interposition, and pre-eclampsia

TABLE I. INCIDENCE OF PREMATURELY BORN AND SURVIVING BABIES, STILLBIRTHS, AND DEATHS DURING THE FIRST MONTH OF LIFE CALCULATED BY YEAR

| YEAR       | NUMBER OF PRE-MATURES | TOTAL NO. OF BABIES BORN | INCIDENCE OF PRE-MATURES PER CENT | PER CENT OF PREMATURES—BY YEAR |          |           |          |                  |          |
|------------|-----------------------|--------------------------|-----------------------------------|--------------------------------|----------|-----------|----------|------------------|----------|
|            |                       |                          |                                   | GRADUATED ALIVE                |          | STILLBORN |          | DIED FIRST MONTH |          |
|            |                       |                          |                                   | CASES                          | PER CENT | CASES     | PER CENT | CASES            | PER CENT |
| 26 (6 mo.) | 6                     | 104                      | 5.8                               | 4                              | 66.7     | 2         | 33.3     | 0                | 00.0     |
| 27         | 19                    | 250                      | 7.6                               | 12                             | 63.1     | 2         | 10.5     | 5                | 26.3     |
| 28         | 19                    | 256                      | 7.4                               | 12                             | 63.1     | 2         | 10.5     | 5                | 26.3     |
| 29         | 23                    | 286                      | 8.0                               | 11                             | 47.8     | 7         | 30.4     | 5                | 21.7     |
| 30         | 25                    | 361                      | 6.9                               | 10                             | 40.0     | 5         | 20.0     | 10               | 40.0     |
| 31         | 43                    | 538                      | 8.0                               | 18                             | 42.0     | 14        | 32.5     | 11               | 25.6     |
| 32         | 46                    | 720                      | 6.4                               | 34                             | 73.9     | 7         | 15.0     | 5                | 11.1     |
| 33         | 65                    | 887                      | 7.3                               | 38                             | 58.5     | 15        | 23.1     | 12               | 18.5     |
| 34         | 82                    | 1,062                    | 7.7                               | 52                             | 63.4     | 19        | 23.2     | 11               | 13.4     |
| 35         | 86                    | 1,234                    | 7.0                               | 55                             | 63.9     | 19        | 22.1     | 12               | 14.0     |
| 36         | 72                    | 1,349                    | 5.3                               | 39                             | 54.2     | 17        | 25.0     | 16               | 22.2     |
| 37         | 55                    | 1,318                    | 4.2                               | 36                             | 65.4     | 12        | 21.8     | 7                | 12.7     |
| 38         | 82                    | 1,724                    | 4.7                               | 49                             | 59.7     | 15        | 18.3     | 18               | 22.0     |
| 39         | 74                    | 1,666                    | 4.4                               | 45                             | 60.8     | 12        | 16.2     | 17               | 23.0     |
| 40         | 99                    | 1,919                    | 5.1                               | 78                             | 77.7     | 9         | 9.1      | 12               | 12.1     |
| 41 (6 mo.) | 65                    | 920                      | 7.1                               | 50                             | 77.0     | 8         | 12.3     | 7                | 10.7     |
| Totals     | 861                   | 14,594                   | 5.9                               | 543                            | 63.1     | 165       | 19.2     | 153              | 17.7     |

*Birth Weight.*—The stillbirth and neonatal mortality data by birth weights, in increments of 250 Gm., are presented in Table II. As anticipated, there were few survivors in the group weighing under 1,250 Gm. (2 pounds and 12 ounces), but the fatality rate decreased rapidly as the birth weight increased.

TABLE II. STILLBIRTH AND INFANT MORTALITY IN RELATION TO BIRTH WEIGHT

| GRAM WEIGHT GROUP | NO. OF CASES | GROSS MORTALITY |          | STILLBIRTHS NO. OF CASES | DIED UNDER ONE MONTH NO. OF CASES | DISCHARGED ALIVE NO. OF CASES |
|-------------------|--------------|-----------------|----------|--------------------------|-----------------------------------|-------------------------------|
|                   |              | NO. OF CASES    | PER CENT |                          |                                   |                               |
| 700- 999          | 39           | 39              | 100      | 23                       | 16                                | 0                             |
| 1,000-1,249       | 37           | 33              | 89.2     | 22                       | 11                                | 3                             |
| 1,250-1,499       | 66           | 51              | 76.7     | 22                       | 29                                | 16                            |
| 1,500-1,749       | 78           | 47              | 60.2     | 16                       | 31                                | 32                            |
| 1,750-1,999       | 125          | 56              | 44.8     | 28                       | 28                                | 70                            |
| 2,000-2,249       | 199          | 43              | 21.6     | 24                       | 19                                | 154                           |
| 2,250-2,499       | 315          | 48              | 15.2     | 29                       | 19                                | 269                           |
| No data           | 2            | 1               | 50.0     | 1                        | 0                                 | 1                             |
| Totals            | 861          | 318             | 36.9     | 165                      | 153                               | 543                           |

*Syphilis.*—Thirteen (31.1 per cent) of the 41 infants born to women with positive serologic reactions were syphilitic, and 9 of the 13 died before discharge, an immediate mortality rate of 61.5 per cent.

*Complications of Pregnancy and Labor.*—The effect of various complications of pregnancy and labor occurring among 263 patients is presented in Table III. In each category the fetal salvage was less than in the uncomplicated cases. Among the 224 patients with nonconvulsive toxemia, labor was induced in only 84. Seven out of 11 women with eclampsia were not induced, whereas all those with placenta previa were started in labor by the procedures utilized to control the bleeding.



*Causes of Fetal and Infant Deaths.*—Among the 318 children, who were stillborn or died during the first month of life, 208 (65.4 per cent) were subjected to post-mortem study, and 218 anatomic diagnoses were given as possible causes of death:

|                                 |     |
|---------------------------------|-----|
| Prematurity (no other findings) | 4   |
| Atelectasis                     | 73  |
| Intracranial hemorrhage         | 44  |
| Congenital anomaly              | 27  |
| Pneumonia                       | 21  |
| Miscellaneous infections        | 9   |
| Subscapular hemorrhage          | 6   |
| Hemoperitoneum                  | 2   |
| Asphyxia (prolapsed cord)       | 2   |
| Undetermined                    | 30  |
| Total                           | 218 |

In four instances no diagnosis other than prematurity could be made, but in the remaining cases there were associated demonstrable pathologic lesions. The high incidences of atelectasis (35.1 per cent) and intracranial hemorrhage (21.2 per cent) were to have been anticipated, since prematurity is known to increase the susceptibility to such conditions. On the other hand, anomalies were probably responsible per se for early delivery. Hemoperitoneum may be blamed on too strenuous efforts at resuscitation by younger staff officers and students who did not recognize the need for gentleness. Subscapular hemorrhage was probably due to the trauma of delivery and deaths from this cause may be attributed to shock. Fifteen of the 21 infants dying from pneumonia were stillborn (1), or died within forty-eight hours (14), and may be presumed to have contracted the infection in utero.

The clinical causes of death in the 110 infants not subjected to post-mortem examination included:

|                                 |     |
|---------------------------------|-----|
| Prematurity                     | 38  |
| Maternal toxemia                | 20  |
| Intracranial hemorrhage         | 15  |
| Placenta previa                 | 13  |
| Syphilis                        | 5   |
| Intercurrent infection (mother) | 3   |
| Abruptio placentae              | 4   |
| Prolapsed cord                  | 2   |
| Undetermined                    | 10  |
| Total                           | 110 |

When "prematurity" alone was diagnosed, there was no reasonable clinical explanation for the early termination of the pregnancy. The parity of the mother did not influence the clinical causes of death among the premature infants, except that placenta previa was more common (12 to 1) among multigravidas in the series, whereas syphilis appeared more frequently in the primigravidas.

#### COMMENT

Any newborn infant weighing less than 2,500 Gm. has an increased chance of being stillborn or of dying during the first year of life. In approximately one-third of the cases, some complication of gestation,

with marked vulval edema, precluding vaginal delivery. These 8 mothers delivered 9 infants, of whom 3 survived (37.5 per cent), while only 6 of the 12 babies born to mothers who were subjected to operation because of previous cesarean section were discharged alive. Five of the children weighed less than 2,000 Gm. and only 2 survived; while among the 12 who weighed between 2,000 and 2,499 Gm., there were 3 stillborn and macerated, 2 that died within three days, and 7 survivors. Such data emphasize again the fact that abdominal delivery is not a child-saving operation, even when there are no maternal complications.

*Duration of Labor.*—The total duration of labor was available for 760 cases. The fetal and infant mortality was greatest (45.3 per cent, or 44 deaths in 97 cases) when parturition lasted less than three hours, and least (29.7 per cent, or 14 deaths in 48 cases) when labor was prolonged more than thirty hours. The two factors which evidently explain this apparently anomalous situation are that rapid labors (1) occurred more commonly with smaller fetuses, and (2) were associated with more extensive fetal damage due to the rapid molding of the head and to the generally greater force of the uterine contractions.

*Sedation and Anesthesia.*—There was no correlation between the type of sedation and the infant survival rate, except in the case of morphine, which was given to 303 mothers. The higher death rate (34.6 per cent) when this drug was exhibited alone or in combination with scopolamine or a barbiturate can be explained by its employment in large doses (gr.  $\frac{1}{2}$  to 3) in patients with severe toxemia. When ordinary sedative doses were given, there was no significant difference in the rates of fetal survival. Some degree of asphyxia was noted in 84 (16.9 per cent) of the 499 cases where no sedative was given, as against 105 (34.6 per cent) of the 362 instances where morphine or some other sedative drug was administered. Among the 208 autopsied infants, there were 21 who showed pneumonia as the probable cause of death; in 16 instances (72.7 per cent) no analgesia had been given the mother.

Some form of anesthesia was given to 733 mothers as follows: ethylene, 477; ethylene and ether, 46; ether, 35; chloroform, 72; cyclopropane, 43; nitrous oxide, 21; nitrous oxide and ether, 5; pudendal block, 15; various others, 19. Among the 82 severely asphyxiated infants, there were 13 cases where no anesthetic had been used, an incidence of 10.0 per cent. By contrast, 45 severely asphyxiated children were born to mothers who received ethylene alone, 9.4 per cent. This would make it seem that the type of anesthetic agent employed played a relatively small role in the production of severe asphyxia.

*Induction of Labor.*—The induction of labor was carried out 251 times, with complete data available for 223 cases; among which there were 125 elective and 98 indicated inductions. The 125 elective inductions represent approximately 0.3 per cent of those carried out over the fifteen-year period, and were regarded as errors in judging the size of the unborn child. By refusing to resort to elective induction until the patient has reached the calculated date of confinement, such mistakes can be materially reduced. There were six twin pregnancies among the 125 in the elective series, and a total mortality of 26 (19.1 per cent) including 11 stillbirths, among the 131 infants. In contrast, the fetal and infant mortality in the indicated inductions was 52.9 per cent, undoubtedly greater because of the higher incidence of more immature infants.

Sedation by the administration of ordinary sedative doses appears not to increase the fetal risk, but larger doses, especially of morphine, with or without other analgesics, double the incidence of asphyxia and add appreciably to the fetal death rate. The type of inhalation anesthetic agent appears not to alter the fetal prognosis significantly, although undoubtedly the depth of anesthesia is a factor; local anesthesia would seem to be preferable.

Induction of labor in itself appears not to prejudice the child, although the condition for which the induction is carried out may alter the outcome unfavorably. Elective induction should obviously be restricted to infants, who are mature both on the basis of menstrual age and of clinical estimation.

Pulmonary atelectasis, intracranial hemorrhage, developmental anomalies, and pneumonia, are, in order, the most frequent causes of fetal or infant death, while toxemia and ante-partum bleeding are the most common clinical causes. Little can be done prophylactically in any of these conditions, except in the case of intracranial hemorrhage, which may possibly be prevented by the administration of vitamin K to the mother before or during labor. The fact that such a large percentage of pneumonia is apparently contracted in utero makes it difficult to combat the infection successfully.

Adequate postnatal care of the prematurely born child still involves the traditional triad of nursery responsibilities: the provision of satisfactory nourishment, the maintenance of proper temperature, and the avoidance of infection, which last is at least partly implemented by the maintenance of high relative humidity.

#### SUMMARY AND CONCLUSIONS

Among 861 consecutive prematurely born children, weighing from 700 to 2,499 Gm., there were 318 (36.9 per cent) who were stillborn or died before the end of the first month, and an additional 36 (4.2 per cent) who died before the end of the first year.

The series included 142 "previable" children weighing less than 1,500 Gm., of whom only 19 (13.4 per cent) survived. Excluding this entire group leaves 719 children with 524 survivors (72.9 per cent) to the end of the first month.

Analysis reveals that there is little possibility, with our present inadequate knowledge, of preventing any significant number of premature births, and that the burden for decreasing the death rate among these infants lies chiefly with improved natal and postnatal care.

The avoidance of other than mild maternal sedation and the use of local anesthesia, together with delivery by spontaneous expulsion or careful forceps extraction following episiotomy appear to offer the best prognosis. The induction of labor, unless indicated by definite medical

such as toxemia, multiple pregnancy, ante-partum bleeding, or intercurrent maternal disease, either leads directly to the early termination of the pregnancy or supplies the medical indication for interruption. In the remainder, the premature birth seems to be brought about by biologic factors of which our knowledge is scant and against which we can offer little protection. In the former group, prenatal care appears to offer very little except in maternal syphilis and in certain cases of toxemia, where there is practically no chronic damage to the vascular or renal apparatus, while in the latter its effects are problematic unless conditions are such that the probable hazards of faulty nutrition, overwork, and endocrine unbalance can be attacked successfully. The chief hope of improving the mortality rate from prematurity at present seems to lie in giving more adequate care to the child that is born before it is fully equipped for extrauterine life. This includes not only postnatal care, but attention to various parturitional factors, which appear to have a potent effect upon the child's chances.

In general, the fate of a prematurely born child depends more upon its actual weight at birth than upon any other factor. This fact forms the basis for the common practice of delaying artificial termination of a pregnancy as long as possible in the face of a disease complication which is best treated by emptying the uterus, as, for example, the toxemias of late pregnancy. It is, however, common knowledge that such a course frequently leads to intrauterine fetal death and thus defeats its own objective. Choice of the proper time for intervention in such cases demands fine judgment for which no acceptable criteria are available.

Syphilis is one disease, the detection and treatment of which during early pregnancy constitutes a distinct triumph for antenatal care. The present tendency toward laws making serologic tests for syphilis compulsory in pregnant women should eventually almost eliminate this disease as a cause of prematurity.

Available data emphasize the importance of the conduct of premature labor in the interests of the child. Rapid delivery, especially that completed within less than three hours, is associated with a high mortality rate, since the premature infant is unable to withstand the forceful uterine contractions incidental to such quick expulsion. Spontaneous delivery with adequate episiotomy is probably the safest, although carefully performed forceps extraction entails little or no additional risk. Delivery of the aftercoming head (breech extraction or podalic version) carries a high risk of fatal injury, largely because of the necessity for rapid cranial molding or of asphyxia due to delay in extracting the relatively large head. Abdominal delivery even in the presence of no serious maternal complications involves such an unexplained mortality as to remove it from the child-saving category.

patients were given the uncoated tablets administered orally before meals, with the exception of certain cases of senile vaginitis in which the tablets were used as vaginal suppositories.

TABLE I. THE INCIDENCE OF NAUSEA PRODUCED BY HEXESTROL

| DAILY DOSE      | NO. PATIENTS TREATED | NO. EXHIBITING NAUSEA |
|-----------------|----------------------|-----------------------|
| Less than 5 mg. | 28                   | 0                     |
| 5 mg.           | 12                   | 0                     |
| 10 mg.          | 19                   | 5                     |
| 15 mg.          | 13                   | 0                     |
| 20 mg.          | 7                    | 1                     |
| 40 mg.          | 1                    | 1                     |
| Total           | 80                   | 7 or 8.75%            |

As can be seen from Table I, the incidence of nausea for all cases is 8.75 per cent. In a previous report of 115 patients treated with stilbestrol under similar conditions, the incidence of nausea was reported as 6.3 per cent, and in those patients receiving 1.0 mg. per day or less, the incidence was 4.1 per cent. Table I clearly indicates that hexestrol will produce nausea, particularly in large doses. Of the 7 patients exhibiting nausea, in only two was it sufficiently severe to be disturbing. These two, evidencing nausea upon 20 and 40 mg. daily, respectively, promptly were relieved when the dose was reduced by one-half. The other 5, all receiving 10 mg. daily, readily established tolerance without reduction of the daily dose in from three to six days.

All 7 patients manifesting nausea with hexestrol were later placed upon 1.0 mg. of diethylstilbestrol daily, and two again developed nausea but 5 did not. Conversely, two patients who have repeatedly become severely nauseated with the administration of 1.0 mg. of stilbestrol daily were changed to 10 mg. of hexestrol daily with complete disappearance of untoward effects and continued relief of symptoms.

Clinical evaluation of the estrogenic activity of hexestrol has been made by a study of its effects upon the menopause, dysmenorrhea, lactation, senile vaginitis and vulvovaginitis in children. Several cases of functional bleeding were treated, but as they are of no value to this report and the results are inconclusive they have not been included.

Thirty-seven menopausal patients, 17 natural and 20 artificial, were given hexestrol. None had previously responded to sedatives alone. Twenty-four responded excellently to the drug, 3 fairly well, and 10 poorly or not at all. A study of 18 of these patients all of whom had at some time previously been treated with natural estrogens or stilbestrol is presented in Table II. Fourteen had recurrence of symptoms after a rest interval of at least four months before hexestrol was begun. Four responded poorly or not at all to stilbestrol and were changed to hexestrol without a rest interval.

The significant feature is that 3 patients who failed to respond to an adequate course of stilbestrol, 1.0 mg. daily for twenty-eight days, reported prompt relief of symptoms when placed on hexestrol. On the other hand, some who responded well to stilbestrol responded poorly or not at all to hexestrol. It is the authors' experience that the dose of hexestrol which will roughly correspond to 1.0 mg. of stilbestrol is 10 mg.

conditions, and attempts to hasten delivery by augmenting the strength of uterine contractions are inadvisable. Abdominal delivery does not give satisfactory fetal salvage and is not to be viewed as a child-saving procedure.

Proper postnatal care involves gentle and adequate resuscitatory measures, small frequent feedings, preferably of breast milk, according to a definite schedule, such as that advanced by Marriott and Jeans (1941), careful regulation of the environment in a modern incubator or premature room with attention not only to the temperature but also to the relative humidity of the air.

When the relative humidity of the nursery was maintained at approximately 50 per cent, and all individuals with upper respiratory infections were excluded, masking and gowning did not materially affect the survival of prematurely born infants.

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## THE ESTROGENIC PROPERTIES OF DIHYDROSTILBESTROL, (HEXESTROL)

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THE new synthetic estrogenic drug diethylstilbestrol is satisfactorily replacing the use of natural estrogens. Since stilbestrol occasionally produces nausea, the authors have searched for an alternative drug which might be equally satisfactory in therapeutic results without this side effect. Bishop and his coworkers<sup>1</sup> reported upon the estrogenic properties of stilbestrol dipropionate and dihydrostilbestrol, called by them hexestrol.\* A similar study of diethylstilbestrol previously reported by the authors<sup>2</sup> has been used for comparison.

The name hexestrol has been used rather than the more descriptive one of dihydrostilbestrol to prevent confusion with diethylstilbestrol. Bishop and his associates found this drug less toxic than stilbestrol and also less potent in estrogenic properties. The dose employed by them was much smaller than that found necessary to give satisfactory results in this study. Details of the structure and synthesis of hexestrol may be found in the above-mentioned article. The following report is concerned chiefly with two factors: so-called toxicity as manifested by nausea, and estrogenic potency as evidenced by clinical results. All

\*Supplied by Eli Lilly and Co. for investigational purposes.

CASE 2.—A 26-year-old colored female was operated upon for an unruptured tubal pregnancy. On the fifth postoperative day the patient developed engorged and painful breasts and began to lactate profusely. She was given 40 mg. of hexestrol daily for three days and experienced considerable relief of the engorgement. She also developed severe nausea and vomiting. The dose was then reduced to 20 mg. daily and at the end of four more days lactation had ceased and the nausea and vomiting had cleared up. Bromsulphthalein and hippuric acid liver function tests were normal at the end of treatment. The patient received a total of 200 mg. in seven days. There was no withdrawal bleeding.

Four patients complaining of senile vaginitis were treated with oral hexestrol. Three received 10 mg. daily for from one to three weeks without response. One received 20 mg. daily for one week with excellent response. The three who had experienced no relief and one other patient who was not given oral therapy were instructed to use a 5 mg. tablet as a vaginal suppository morning and night. In all 4, an atrophic, ulcerated vaginal mucosa was converted to a thick, more normal, one with relief of symptoms at the end of a week of treatment. The local response was not as marked as that usually observed under the influence of amniotin perles of 1,000 I.U. each, and in contrast the thickened mucosa produced by hexestrol was observed to be rather dry and furry in appearance without much desquamation.

Twelve children with gonococcal vulvovaginitis received oral hexestrol. The results are presented in Table IV. Two of these patients developed slight bilateral breast hypertrophy on 1.0 and 2.0 mg. daily for seven days, respectively. This subsided in both within four weeks after the drug was discontinued. This small series of children compares more than favorably with a similar series treated with oral diethylstilbestrol in identical dose and previously reported by the authors.<sup>3</sup> It is even suggested that hexestrol may have a more selective action upon the pre-pubertal vaginal mucosa than does stilbestrol.

TABLE IV. RESULTS OF VULVOVAGINITIS TREATED WITH HEXESTROL ORALLY

| AGE | DAILY<br>MG. DOSE | TOTAL<br>MG. DOSE | RESULTS IN TERMS OF VAGINAL SMEAR AND PH            |
|-----|-------------------|-------------------|---|
| 2   | 1.0               | 7.0               | Negative smear, pure adult epithelium and pH of 4.5 |
| 5   | 1.0               | 7.0               | Negative smear, pure adult epithelium and pH of 4.5 |
| 2   | 1.0               | 7.0               | Negative smear, pure adult epithelium and pH of 6.0 |
| 2   | 1.0               | 7.0               | Negative smear, pure adult epithelium and pH of 4.5 |
| 2   | 1.0               | 14.0              | Negative smear, pure adult epithelium and pH of 4.5 |
| 11½ | 1.0               | 14.0              | Negative smear, pure adult epithelium and pH of 4.5 |
| 2   | 1.0               | 14.0              | Negative smear, pure adult epithelium and pH of 4.5 |
| 8   | 2.0               | 14.0              | Negative smear, pure adult epithelium and pH of 4.5 |
| 8   | 2.0               | 14.0              | Negative smear, pure adult epithelium and pH of 4.5 |
| 6   | 2.0               | 14.0              | Negative smear, pure adult epithelium and pH of 4.5 |
| 5   | 2.0               | 20.0              | Negative smear, pure adult epithelium and pH of 4.5 |
| 7   | 2.0               | 28.0              | Negative smear, pure adult epithelium and pH of 4.5 |

A few patients exhibited other untoward effects aside from nausea. Exclusive of the patients with an artificial menopause and with functional uterine bleeding of 43 patients who were given oral hexestrol withdrawal bleeding was noted in 4, or 9.3 per cent. None of these exhibited any bleeding during the administration of the drug. This compares well with a similar series of 99 patients treated with diethylstilbestrol in whom the incidence of bleeding was 13.9 per cent. Breast discomfort was noted in two of the 37 menopausal patients during

TABLE II. COMPARISON OF EFFECTS OF STILBESTROL AND DIHYDROSTILBESTROL

| STILBESTROL<br>DAILY MG. DOSE                                  | RESPONSE               | HEXESTROL<br>DAILY MG. DOSE | RESPONSE               |
|--|------------------------|-----------------------------|------------------------|
| 1.0  | Excellent              | 1.0                         | None                   |
| 1.0  | Poor                   | 1.0                         | Excellent              |
| 1.0  | Excellent              | 3.0                         | Excellent              |
| 1.0  | Excellent              | 4.0                         | Fair                   |
| 1.0  | Excellent              | 4.0                         | Fair                   |
| 1.0  | Excellent              | 4.0                         | None                   |
| 1.0  | Excellent              | 5.0                         | None                   |
| 1.0  | Poor                   | 5.0                         | Fair                   |
| 1.0  | Excellent              | 6.0                         | None                   |
| 1.0  | Excellent              | 10.0                        | Excellent              |
| 1.0  | Excellent              | 10.0                        | Excellent              |
| 1.0  | Excellent              | 10.0                        | Excellent              |
| 1.0  | None                   | 10.0                        | Excellent              |
| 1.0  | None                   | 15.0                        | Excellent              |
| 1.0  | Excellent              | 15.0                        | None                   |
| 1.0  | Excellent              | 20.0                        | Excellent              |
| Natural Estrogen<br>Total Dose<br>120,000 I.U.<br>120,000 I.U. | Excellent<br>Excellent | 2.0<br>4.0                  | Excellent<br>Excellent |

Eight patients with primary dysmenorrhea were treated with hexestrol. Three were also given stilbestrol for purposes of comparison. The regular practice in the endocrine clinic of the department of gynecology is to administer a daily dose for fourteen successive days, beginning with the first day of menstruation. The effect is then noted upon the following period. The results are reported in Table III. The first 4 patients were treated for two successive cycles with the drugs in the order listed.

TABLE III. RESULTS IN TREATMENT OF DYSMENORRHEA

| CASE | DRUG USED   | DAILY DOSE | RESPONSE  |
|------|-------------|------------|-----------|
| 1    | Hexestrol   | 3.0 mg.    | Fair      |
|      | Stilbestrol | 1.0 mg.    | Excellent |
| 2    | Hexestrol   | 2.0 mg.    | None      |
|      | Stilbestrol | 1.0 mg.    | Excellent |
| 3    | Hexestrol   | 5.0 mg.    | None      |
|      | Stilbestrol | 1.0 mg.    | None      |
| 4    | Hexestrol   | 1.0 mg.    | None      |
|      | Hexestrol   | 5.0 mg.    | Excellent |
| 5    | Hexestrol   | 10.0 mg.   | Excellent |
| 6    | Hexestrol   | 10.0 mg.   | Excellent |
| 7    | Hexestrol   | 15.0 mg.   | Excellent |
| 8    | Hexestrol   | 15.0 mg.   | Excellent |

Hexestrol was administered to two patients for the suppression of lactation. These are reported as such.

CASE 1.—A 17-year-old colored female, six months post partum, was lactating freely from both breasts although she had stopped nursing her child two weeks prior. She had had no menses since previous to the onset of her pregnancy. Twenty milligrams of hexestrol were administered daily for seven days at the end of which time lactation ceased in both breasts. Three days after the drug was discontinued the patient menstruated for two days.



# VAGINAL TRICHOMONIASIS\*

## COMPLEMENT FIXATION, PUERPERAL MORBIDITY, AND EARLY INFECTION OF NEWBORN INFANTS

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### COMPLEMENT FIXATION

LITTLE is known of the serologic phenomena which develop in response to vaginal trichomonads. Wendlberger,<sup>10</sup> using an alcoholic extract of an impure culture of the protozoa as antigen, demonstrated complement fixing reactions in 22 of 32 infected women. Sixteen uninfected women gave negative reactions, as did carriers with no manifestations of vaginal disease. The 22 women who gave reactions had abnormal discharges, with or without vaginitis.

Four hundred consecutive obstetric patients admitted to the University Hospital were studied ante and post partum by "hanging drop" and culture techniques for *Trichomonas vaginalis* as a necessary preliminary to the evaluation of the complement fixation tests.

For the examination of fresh specimens discharge from the lower vagina and from the posterior fornix was collected on sterile cotton applicators which were agitated in small tubes containing 1 c.c. of Ringer's solution. The suspensions were spread on glass slides and examined promptly for motile trichomonads under the low-power lens system. Cultures were made by placing similar applicators coated with discharge from the same areas into tubes of 5 per cent human serum in Locke's solution over placenta infusion agar.<sup>11</sup> The sediment in the bottom of the tubes was examined within twenty-four hours for motile protozoa.

Material was obtained from the lower vagina and posterior fornix before delivery and from the lower vagina post partum. The results, as tabulated in Table I, indicate a slight superiority of examination of fresh vaginal discharge over the culture technique. On the other hand a few specimens revealed trichomonads only in culture.

It is believed that examination of fresh vaginal discharge is adequate for routine diagnosis. Cultures are employed routinely in this clinic but their chief value lies in demonstrating the organisms in an occasional patient under treatment in whom examination of the fresh discharge is negative. The disadvantages lie in the preparation of the media, which is simple but time consuming, and in the fact that twenty-four hours must elapse before the results can be obtained.

\*This report is an extension of a study of *Trichomonas vaginalis* Donné which has been in progress for several years.<sup>1-3</sup>

treatment. This discomfort quickly disappeared when the drug was discontinued. No other untoward effects of the drug were noticed.

#### CONCLUSIONS

Hexestrol is a potent synthetic estrogenic drug. It may be satisfactorily substituted for diethylstilbestrol in an attempt to overcome nausea or to produce a better clinical response in a patient resistant to the latter drug. When used in sufficient dose it may produce nausea. This is milder than that produced by comparable doses of stilbestrol and responds quickly to reduction of the amount administered. The effective dose in adults has been found to be about ten times that of diethylstilbestrol. In children, oral hexestrol is, if anything, more effective than oral stilbestrol in equal dose when used to treat vulvovaginitis. The authors recommend that this drug be given extensive trial as an alternative drug to diethylstilbestrol.

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Yerushalmy, Gardiner and Palmer: *Studies in Childbirth Mortality. III. Puerperal Fatality in Relation to Mother's Previous Infant Losses*, Pub. Health Rep. 56: 1463, 1941.

This paper deals with puerperal fatality and late fetal and neonatal mortality in their relation to the mother's previous infant losses. Among others, the following findings are recorded:

Of the 161,177 births of orders two and over entering into this study, 76.9 per cent were to mothers whose previous issue had all survived and 23.1 per cent were to mothers who had lost one or more previous children.

The rates of loss of both mother and infant were about twice as high in the group with a history of previous loss as in the group with no previous loss.

The higher the number of previous losses to the mother, the greater was the chance of death to both mother and infant. The increase with advancing number of previous losses was more pronounced for the loss of offspring than it was for the loss of mother.

The higher rates for puerperal fatality and for infant loss associated with previous losses were present to a considerable degree in the premature as well as in the full-term deliveries. The puerperal fatality rate for full-term deliveries was 16.0 among mothers with no history of previous losses and 25.8 among mothers who had lost one or more of their previous children. The corresponding rates among the premature deliveries were 134.1 and 179.4, respectively. Similarly, the late fetal and neonatal mortality rates were 20.0 and 47.1 among full-term births and 501.4 and 670.0 among the premature.

The suggestion is made that the father also may play an important part in these cases of repeated losses in the family.

as typhoid fever from which a patient may completely recover and be free from the offending organisms but still give positive serologic reactions. There is no evidence to oppose a similar possibility for vaginal trichomoniasis. Such a hypothesis would explain positive reactions in women in whom no trichomonads could be demonstrated; they may have been infected but have undergone spontaneous cure. Cross reactions with oral and intestinal trichomonads have not been excluded.

No practical importance is attached to the demonstration of complement fixing reactions at this time. Certainly the test is of no diagnostic value, and it remains to be seen whether there is any correlation with spontaneous or therapeutic cure.

#### PUERPERAL MORBIDITY

It has long been the contention of certain investigators that *Trichomonas vaginalis* in the pregnant woman is a source of danger during the puerperium and many advocate treatment of the infection during pregnancy as a prophylactic measure. If trichomonads are a provocative factor in puerperal febrile morbidity a study of the puerperal records of a large series of women in whom the presence or absence of trichomonads has been established should offer evidence of such action. With this in mind the post-partum temperature data on 880 women delivered in this clinic have been reviewed and the results listed in Table IV.

TABLE IV. PUERPERAL FEBRILE MORBIDITY; 880 OBSTETRIC PATIENTS

|                                      | ONE DAY FEVER | MORBID<br>PUERPERIUM | TOTAL<br>PATIENTS |
|--------------------------------------|---------------|----------------------|-------------------|
| Patients with <i>T. vaginalis</i>    | 32, or 14.3%  | 19, or 8.5%          | 223               |
| Patients without <i>T. vaginalis</i> | 87, or 11.7%  | 55, or 8.3%          | 657               |

The significance of one-day fever is not understood, but it is doubtful whether its slightly higher incidence in association with the presence of *T. vaginalis* could be attributed to the abnormal bacterial flora usually present with this vaginal infection. It is obvious that women with *T. vaginalis* have no increased tendency to prolonged fever during the puerperium.\*

These data support the idea that vaginal trichomoniasis in pregnancy should not necessarily be treated, unless associated vulvovaginitis produces discomfort.

#### NATURAL TRANSMISSION TO BABIES

There are undoubtedly multiple modes of transmission of *Trichomonas vaginalis*. Cross contamination from one woman to another and sexual intercourse probably play major roles. Early childhood

\*Post-partum temperatures were taken every four hours. One-day fever is defined as a temperature of 100.4° or more occurring during any single day after the first twenty-four hours. Morbid puerperium is defined as one in which the temperature reaches 100.4° or more during two or more days.

TABLE I. COMPARISON OF "HANGING DROP" AND CULTURE TECHNIQUES FOR THE DIAGNOSIS OF *TRICHOMONAS VAGINALIS*\*

|              | 76 PATIENTS POSITIVE BOTH ANTE AND POST PARTUM |           |           |           |                    | 18 PATIENTS POSITIVE ONLY ANTE PARTUM |           |           |           | 16 PATIENTS POSITIVE ONLY POST PARTUM |           |           |           |
|--------------|--|-----------|-----------|-----------|--------------------|---------------------------------------|-----------|-----------|-----------|---------------------------------------|-----------|-----------|-----------|
|              | HD+<br>C+                                      | HD-<br>C+ | HD+<br>C- | HD-<br>C- | No<br>Cul-<br>ture | HD+<br>C+                             | HD-<br>C+ | HD+<br>C- | HD-<br>C- | HD+<br>C+                             | HD-<br>C+ | HD+<br>C- | HD-<br>C- |
| Vagina       | 55   | 2         | 16        | 3         | -                  | 11                                    | 1         | 6         | -         | -                                     | -         | -         | 16        |
| Post. Fornix | 55   | 3         | 12        | 6         | -                  | 12                                    | 1         | 2         | 3         | -                                     | -         | -         | 16        |
| Post partum  | 59   | 4         | 7         | -         | 6                  | -                                     | -         | -         | 18        | 14                                    | 2         | -         | -         |

\*HD, Hanging drop; C, culture.

Ante-partum venous blood specimens were tested for the presence of complement-fixing antibodies by the technique of Kolmer.<sup>12</sup> A bacteria-free suspension of *Trichomonas vaginalis*<sup>1, 2</sup> in physiologic saline solution was used as antigen. These organisms were grown in a simple peptone human-serum carbohydrate medium and were repeatedly washed before use, thus insuring an antigen in which the only complex elements foreign to the human body were the components of the trichomonads.

The results are presented in Table II. Patients infected with *Trichomonas vaginalis* were three times as likely to have positive serologic reactions as were uninfected women.

TABLE II. COMPLEMENT FIXATION DATA

| FOUR HUNDRED ANTE-PARTUM OBSTETRIC PATIENTS |        |                              |          |
|---|--------|------------------------------|----------|
|   | NUMBER | POSITIVE COMPLEMENT FIXATION |          |
|   |        | NUMBER                       | PER CENT |
| Trichomonas positive                        | 110    | 52                           | 47.27    |
| Trichomonas negative                        | 290    | 48                           | 16.55    |

Reclassification of 399 of these patients on the basis of objective vaginal changes present at sterile ante-partum speculum examination gives the results shown in Table III. These data indicate that patients with abnormal discharge and/or vaginal inflammation are more likely to give positive complement fixation reactions, but that there was a considerable percentage of reactors among patients with no objective pathologic changes in the vagina. This contradicts the findings of Wendlberger but is more in line with what might be expected from an immunologic point of view. There are many infectious diseases such

TABLE III

| TRICHO-<br>MONAS | NO. | ABNORMAL DISCHARGE |      |        |      | ABNORMAL DISCHARGE AND/OR INFLAMMATION |      |        |      | NORMAL DISCHARGE AND MUCOSA |      |        |      |
|------------------|-----|--------------------|------|--------|------|--|------|--------|------|-----------------------------|------|--------|------|
|                  |     | NO.                | %    | C. F.* | %    | NO.                                    | %    | C. F.* | %    | NO.                         | %    | C. F.* | %    |
| Positive Present | 109 | 65                 | 59.6 | 32     | 49.1 | 28                                     | 25.6 | 13     | 46.4 | 16                          | 14.6 | 6      | 37.5 |
| Negative Absent  | 290 | 184                | 63.4 | 37     | 20.1 | 23                                     | 7.9  | 3      | 13.0 | 83                          | 28.6 | 8      | 9.6  |

\*C.F., Positive complement fixation.

## METHODS FOR THE OBJECTIVE EVALUATION OF ESTROGEN THERAPY IN THE MENOPAUSE\*

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AS ENDOCRINE therapy has become established as a reliable part of the physician's armamentarium, there has been a concomitant effort to devise objective laboratory tests whereby the therapeutic uses of endocrine preparations may be controlled accurately. In dysfunctions of the thyroid gland the basal metabolic rate has been found a dependable index of thyroid activity. In diabetes mellitus, the blood and urinary sugar levels have proved invaluable guides in regulating insulin dosage. As the principle of estrogen replacement therapy has become accepted as sound in the management of menopausal patients, the need for similarly reliable objective checks on estrogen therapy has become apparent. In the menopausal syndrome, perhaps more so than in any other endocrine disorder, there is quite often an admixture of psychologic difficulty, social maladjustment, and actual organic disease co-existing with symptoms of estrogen deficiency. The conscientious practitioner is, therefore, confronted with the often difficult problem of evaluating properly the extraendocrine factors, and of giving his patient the benefit of sufficient estrogen therapy at the same time.

Unfortunately no single laboratory test has yet been devised whereby the adequacy of estrogen replacement therapy in the menopause may be objectively evaluated with accuracy. By the utilization of certain physiologic facts, however, it is easily possible to demonstrate the existence of estrogen deficiency and to estimate roughly the extent of estrogen activity resulting from estrogen therapy. For these purposes several methods of checking have been developed including observation of histologic changes in vaginal smears and biopsies, observation of histologic changes in endometrial biopsies, and determination of the levels of estrogenic substance and follicle-stimulating hormone in the blood and urine.

These methods have been used by various investigators in establishing the relationship between estrogen deficiency and the typical vasomotor symptoms of the menopausal syndrome, in proving the potency of natural and synthetic estrogen preparations, and in determining the relative efficiency of various routes and forms of estrogen administration. In this way they have been of value.

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infections can usually be explained on the basis of contamination, but the possibility exists that female babies born to infected mothers may become infected during birth. With this possibility in mind, 41 such babies were examined within the first eight days of life. Hanging drop preparations were made from the vagina and introitus, usually on the fourth and eighth days, although in some instances only one examination was undertaken. Two babies (4.8 per cent) were found infected; in both the first examination was negative but the second revealed motile trichomonads, including dividing forms. Since the babies could not be followed for more than eight days, the duration of their infections is unknown. It is not illogical to assume that the trichomonads can exist for many years as a latent infection in young children as is known to be true in adult women. On the other hand, changing biologic conditions in the infant vagina, notably a shift in pH, may militate against persistence of the infection.

#### SUMMARY

Examination of fresh vaginal discharge is the more practical and economical way to diagnose the presence of *Trichomonas vaginalis*. Cultures are highly satisfactory but add little to the study.

Approximately 50 per cent of women infected with *T. vaginalis* gave positive complement fixation reactions, which were noted less often in carriers than in women with vaginitis. One-sixth of women in whom *Trichomonas vaginalis* could not be demonstrated also gave positive reactions. It is not improbable that some of these women had been previously infected.

*Trichomonas vaginalis* infection is not associated with an increase in puerperal morbidity and its presence does not constitute an indication for treatment in asymptomatic patients.

Approximately 5 per cent of female babies born to infected mothers were shown to be infected with *Trichomonas vaginalis* during the first eight days of life.

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estrogen therapy, we have resummarized our data in Table II. Here it is seen that the percentage of patients in whom the results of estrogen therapy are unsatisfactory varies directly with the urinary estrogen level present before treatment. Those who excreted normal amounts of urinary estrogen before treatment were less likely to be relieved of their symptoms than those who excreted none or only small amounts.

We have used the same assay method as formerly.<sup>9</sup>

TABLE II. RELATIONSHIP BETWEEN PRETREATMENT LEVEL OF URINARY ESTROGEN IN 64 MENOPAUSAL PATIENTS WITH SYMPTOMS AND THE RESULTS OF SUBSEQUENT ESTROGEN THERAPY

| PRETREATMENT URINARY ESTROGEN LEVEL | NO. OF PATIENTS | RESULTS OF SUBSEQUENT ESTROGEN THERAPY |                        |                |
|-------------------------------------|-----------------|--|------------------------|----------------|
|                                     |                 | SATISFACTORY                           | PARTIALLY SATISFACTORY | UNSATISFACTORY |
| 0 to 3 R.U./24 hr.                  | 46              | 71.7%                                  | 23.9%                  | 5.4%           |
| 3 to 10 R.U./24 hr.                 | 14              | 57.1%                                  | 28.6%                  | 14.3%          |
| Over 10 R.U./24 hr.                 | 4               | 0                                      | 50.0%                  | 50.0%          |

#### URINARY CONTENT OF FOLLICLE-STIMULATING HORMONE

Failure of ovarian function at the menopause is associated with or followed by an increase in the blood and urinary content of gonadotropic hormone secreted by the anterior lobe of the hypophysis. There has been rather general agreement that a demonstrable excess of gonadotropic hormone is usually present in menopausal patients,<sup>1-9</sup> and some have felt that a correlation between this excess and the typical vasomotor symptoms exists.<sup>3-7</sup> Others disagree.<sup>8</sup> To add to the confusion, some investigators report that the gonadotropic hormone diminishes or disappears during adequate estrogen therapy<sup>3-5, 9</sup> while others find no such change<sup>7, 8</sup> even with estrogen dosage sufficient to relieve the subjective symptoms.

TABLE III. RESULTS OF 289 URINARY GONADOTROPIC HORMONE ASSAYS IN 60 MENOPAUSAL WOMEN

|   | NO. OF SPECIMENS | 0 R.U./LITER | 25 R.U./LITER | OVER 50 R.U./LITER |
|---|------------------|--------------|---------------|--------------------|
| <i>Untreated Menopausal Patients</i>        |                  |              |               |                    |
| Patients with symptoms                      | 78               | 47.4%        | 33.3%         | 19.3%              |
| Patients without symptoms                   | 20               | 60.0%        | 35.0%         | 5.0%               |
| <i>Estrogen-Treated Menopausal Patients</i> |                  |              |               |                    |
| Patients with symptoms                      | 56               | 46.6%        | 23.2%         | 30.2%              |
| Patients without symptoms                   | 135              | 83.7%        | 11.1%         | 5.2%               |

In Table III are summarized the results of 289 urinary gonadotropic hormone assays on 60 menopausal women, with and without symptoms, treated and untreated. In this table "0" indicates less than 25 R.U./liter, "25" represents more than 25 but less than 50 R.U./liter,

Furthermore it would seem that one or the other of these laboratory procedures might be useful to the clinician as an aid in selecting those menopausal patients most likely to benefit from estrogen therapy and in guiding him in regulating the estrogen regime for the individual patient. It is for the purpose of evaluating these tests in terms of clinical usefulness that this study has been undertaken.

#### URINARY CONTENT OF ESTROGENIC SUBSTANCES

Failure of ovarian function is now almost universally accepted as the primary cause of the menopause. This ovarian failure with marked impairment, if not total loss, of estrogen supply has formed the basis for the rationale of estrogen replacement therapy. Since this is the case, it might logically be expected that patients with menopausal symptoms would have an absence or very low level of estrogenic substance in the urine, and that an increase of the estrogen to normal levels would go hand-in-hand with a disappearance of menopausal symptoms.

TABLE I. RESULTS OF 324 URINARY ESTROGEN ASSAYS IN 80 MENOPAUSAL WOMEN

|   | NO. OF<br>SPECIMENS | 0 TO 3 R.U.<br>/24 HOURS | 3 TO 10 R.U.<br>/24 HOURS | OVER 10 R.U.<br>/24 HOURS |
|---|---------------------|--------------------------|---------------------------|---------------------------|
| <i>Untreated Menopausal Patients</i>        |                     |                          |                           |                           |
| Patients with symptoms                      | 79                  | 70.9%                    | 22.8%                     | 7.3%                      |
| Patients without symptoms                   | 17                  | 64.7%                    | 35.3%                     | 0                         |
| <i>Estrogen-Treated Menopausal Patients</i> |                     |                          |                           |                           |
| Patients with symptoms                      | 76                  | 9.2%                     | 77.6%                     | 13.2%                     |
| Patients without symptoms                   | 152                 | 3.3%                     | 75.7%                     | 21.0%                     |

In Table I are summarized the results of 324 urinary estrogen assays on 80 menopausal patients with and without symptoms, before and during therapy with estrogenic substances. By way of explanation, it should be said that 0 to 3 R.U./twenty-four hours represents in our laboratory practically no detectable estrogenic substance; 3 to 10 R.U./twenty-four hours represents the lower range and 10 to 20 R.U./twenty-four hours the upper range for normally menstruating women.

It is surprising to find that the assay values in our untreated menopausal women fall into similar percentage groups whether or not the patients are having menopausal symptoms and, in those patients who have received estrogen therapy, the same general percentage distribution obtains for the symptomatic and asymptomatic alike. So, while most of the untreated patients show a definite estrogen deficiency and while most of the estrogen-treated patients show quantities of urinary estrogen comparable to those found in normally menstruating women, there apparently is no correlation between the amount of estrogen in the urine and the presence or absence of menopausal symptoms.

In order to find out if urinary estrogen levels might be of value in predicting which symptomatic patients would most likely benefit from



TABLE V. RESULTS OF 124 VAGINAL SMEARS IN 62 MENOPAUSAL WOMEN

|   | NO. OF<br>SPECI-<br>MENS | TYPE I | TYPE II | TYPE III | TYPE IV |
|---|--------------------------|--------|---------|----------|---------|
| <i>Untreated Menopausal Patients</i>        |                          |        |         |          |         |
| Patients with symptoms                      | 44                       | 25.0%  | 38.6%   | 29.5%    | 7.9%    |
| Patients without symptoms                   | 7                        | 0      | 42.9%   | 42.9%    | 14.2%   |
| <i>Estrogen-Treated Menopausal Patients</i> |                          |        |         |          |         |
| Patients with symptoms                      | 26                       | 23.1%  | 11.6%   | 42.2%    | 23.1%   |
| Patients without symptoms                   | 47                       | 0      | 8.5%    | 41.7%    | 49.8%   |

be seen that there is a definite tendency for patients without symptoms, whether treated or untreated, to show more evidence of estrogen stimulation than those patients who are having symptoms. However, it is equally apparent that patients may be without symptoms and still show vaginal smear evidence of estrogen deficiency, while other patients still having symptoms may show vaginal smear evidence of adequate estrogen stimulation.

TABLE VI. RELATIONSHIP BETWEEN PRETREATMENT VAGINAL SMEAR TYPE IN 25 MENOPAUSAL PATIENTS WITH SYMPTOMS AND THE RESULTS OF SUBSEQUENT ESTROGEN THERAPY

| PRETREATMENT<br>VAGINAL SMEAR<br>TYPE | NO. OF<br>PATIENTS | RESULTS OF SUBSEQUENT ESTROGEN THERAPY |                           |                |
|---------------------------------------|--------------------|--|---------------------------|----------------|
|                                       |                    | SATISFACTORY                           | PARTIALLY<br>SATISFACTORY | UNSATISFACTORY |
| Type I                                | 4                  | 75.0%                                  | 25.0%                     | 0              |
| Type II                               | 11                 | 63.7%                                  | 27.3%                     | 9.0%           |
| Type III                              | 10                 | 50.0%                                  | 50.0%                     | 0              |
| Type IV                               | 0                  | -----                                  | -----                     | ----           |

In Table VI the pretreatment vaginal smear types in 25 cases are charted against the clinical results of subsequent estrogen therapy. Here it is seen that in general the greater the estrogen deficiency, as indicated by the vaginal smear type, the greater the likelihood that satisfactory results will be obtained with estrogens.

#### CERVICAL MUCUS

Utilization of still another method for estimating the adequacy of estrogen therapy in the menopause has been reported by Guttmacher and Shettles<sup>18</sup> who found that definite, readily demonstrable changes occur in the cervical mucus when the menopausal patient is treated with estrogens. These changes were found to simulate the cyclic changes in the character of the cervical mucus occurring regularly during menstrual life,<sup>19-21</sup> as regards the following factors: amount, pH, viscosity, turbidity, cellular content, penetrability by spermatozoa in vitro, and survival time of spermatozoa in contact with the mucus in vitro. In the untreated menopausal woman, the cervical mucus is quite scanty, has a pH of 4.0 to 6.0, is highly viscous or crumbly in character, is cloudy

and "more than 50 R.U./liter" is self-explanatory. Examination of this table shows a rather general correlation between symptoms and gonadotropic excess, present in both treated and untreated groups, but more definite in the former where almost 85 per cent of assays in asymptomatic treated patients show an absence of the gonadotropic factor.

TABLE IV. RELATIONSHIP BETWEEN PRETREATMENT LEVEL OF URINARY GONADOTROPIC HORMONE IN 50 MENOPAUSAL PATIENTS WITH SYMPTOMS AND THE RESULTS OF SUBSEQUENT ESTROGEN THERAPY

| PRETREATMENT URINARY<br>GONADOTROPIC HORMONE LEVEL | NO. OF<br>PATIENTS | RESULTS OF SUBSEQUENT<br>ESTROGEN THERAPY |                                |                     |
|--|--------------------|---|--------------------------------|---------------------|
|  |                    | SATISFAC-<br>TORY                         | PARTIALLY<br>SATISFAC-<br>TORY | UNSATISFAC-<br>TORY |
| 0 R.U./liter                                       | 26                 | 73.1%                                     | 26.9%                          | 0                   |
| 25 R.U./liter                                      | 13                 | 61.5%                                     | 30.7%                          | 8.8                 |
| Over 50 R.U./liter                                 | 11                 | 72.7%                                     | 27.3%                          | 0                   |

In Table IV these data are rearranged to show whether or not determination of the urinary gonadotropic hormone level before treatment would aid in predicting which patients would be likely to benefit from estrogen therapy. It is of interest to note that only one-half of the patients showed a gonadotropic excess before treatment. Analysis of the results of subsequent estrogen therapy reveals that one group fared as well as another. Therefore there seems to be no correlation between the pretreatment level of gonadotropic hormone and the subsequent success or failure of estrogen therapy.

We have used the same assay method as formerly.<sup>9</sup>

#### VAGINAL SMEARS

Papanicolaou and Shorr<sup>10</sup> have demonstrated that the vaginal smear in the menopausal woman typically shows atrophic changes with large numbers of leucocytes, erythrocytes, and small epithelial cells of the basal type. They were able to demonstrate that with adequate estrogen therapy the vaginal smear could be changed to the estrous type with a predominance of cornified epithelial cells, and an absence of leucocytes, erythrocytes, and the small basal epithelial cells. The opinion was set forth that these vaginal smear changes correspond rather closely with the state of subjective menopausal symptoms, and that the vaginal smear method, therefore, offers a reliable means of regulating estrogen therapy. Other investigators have subsequently utilized this procedure with varying degrees of confirmation.<sup>11-17</sup>

In Table V are summarized the results of 124 vaginal smears in 62 menopausal women, treated and untreated, with and without symptoms. The terms Type I, II, III, and IV represent progressive trophic changes from the completely atrophic type to the full estrous type. It will

per day, no change occurred in the cervical mucus though these patients improved clinically. In general subjective improvement corresponded with changes in the cervical mucus but exceptions did occur.

#### SUMMARY AND CONCLUSIONS

Four objective methods for determining the adequacy of estrogen therapy in the menopause have been considered for the purpose of evaluating their clinical usefulness. Our data, in agreement with reports of others, show that, in general, menopausal patients have little if any estrogenic substance in the urine, have increased amounts of gonadotropic hormone in the urine, show atrophic changes in the vaginal smear, and secrete a scanty, viscid, cellular mucus from the cervical glands. In patients adequately treated with estrogens the urinary level of estrogenic substance usually rises to the levels found in menstrual life; the urinary gonadotropic hormone often decreases or disappears; the vaginal smear typically changes to the estrous type; and the cervical glands secrete abundant, clear, alkaline, acellular mucus. However, we have also shown that the asymptomatic patient may still show objective evidence of estrogen deficiency and that the patient with symptoms may show evidence of estrogen activity. Though these cases are exceptions, they are also numerous. Therefore, we do not believe that the amount of estrogen necessary to increase the urinary output of estrogen to normal levels, to depress the elaboration of gonadotropic hormone, to change the vaginal smear to the estrous type, or to stimulate the activity of the cervical glands, is necessarily the same amount of estrogen that will be required to alleviate the vasomotor symptoms of the menopause.

While not intending to minimize in any way the value of these tests in investigative work, it is our opinion that in the regulation of estrogen therapy for the individual patient they are not sufficiently dependable to serve as crucial criteria, but should rather be looked upon as supplemental aids. We agree with Novak<sup>22</sup> who says, "On the whole . . . [the] vasomotor symptoms offer the best criterion as to the severity of the climacteric and as to the efficacy or inefficacy of therapeutic measures."

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white or yellow, contains many leucocytes and epithelial cells, is not penetrable by spermatozoa in vitro, and immobilizes spermatozoa immediately by contact. At the height of estrogen stimulation the cervical mucus becomes very abundant, flowing from the external os, has a pH of 7.5 to 8.5, is fluid-like with low viscosity, is glairy and transparent, is almost cell free, is readily penetrable by spermatozoa, and, when in contact with spermatozoa in vitro at room temperature, allows their survival for as long as twenty-four hours, even longer than their survival time in seminal plasma. Dr. L. B. Shettles has carried out complete examinations of specimens of cervical mucus from 25 of our symptomatic menopausal patients before treatment and from 41 menopausal patients who were at the time receiving estrogen therapy. The results in a portion of these cases have been included in the report of Guttmacher and Shettles.<sup>18</sup>

TABLE VII. CHARACTERISTICS OF THE CERVICAL MUCUS IN MENOPAUSAL PATIENTS BEFORE AND AFTER ESTROGEN THERAPY

| CHARACTERISTICS OF CERVICAL MUCUS     | UNTREATED MENOPAUSAL PATIENTS (25 CASES) | PATIENTS TREATED WITH 0.1 TO 0.2 MG. STILBESTROL Q.D. (10 CASES) | PATIENTS TREATED WITH 1.0 MG. OR MORE STILBESTROL Q.D. (20 CASES) | PATIENTS TREATED WITH SUBCUTANEOUS ESTROGENIC PELLETS (5 CASES) |
|---------------------------------------|--|--|---|---|
| Amount                                | Scanty                                   | Moderate   | Abundant  | Abundant  |
| pH                                    | 4.0-6.0                                  | 6.0-7.0  | 7.0-8.5   | 7.0-8.5   |
| Viscosity                             | Tenacious                                | Slightly tenacious   | Fluid-like  | Fluid-like  |
| Turbidity                             | Milky                                    | Moderately cloudy  | Transparent, glairy   | Transparent, glairy   |
| Cellular content                      | Many leucocytes and epith. cells         | Moderate leucocytes and epith. cells                             | Almost cell-free  | Almost cell-free  |
| Penetrability by spermatozoa in vitro | None                                     | Slight   | Readily penetrable  | Readily penetrable  |
| Survival time of spermatozoa in vitro | None                                     | One-half hour or less  | As long as 24 hours   | As long as 24 hours   |

NOTE: In 6 patients treated with oral stilbestrol, 0.1 to 1.0 mg. q.d., the cervical mucus did not change from the type found in the untreated menopausal patient.

The results in all cases are summarized in Table VII. The untreated patients uniformly showed scanty, cellular, tenacious mucus. Patients treated with small oral doses of stilbestrol showed, as a rule, increased amounts of mucus with higher pH and fewer cells, while those receiving 1.0 or more of stilbestrol per day and those implanted subcutaneously with estrogenic pellets showed the maximal change with abundant, flowing mucus which was glairy and transparent with a high pH, and almost no cellular elements. Several of these latter patients actually complained of "leucorrhea," and in each case examination showed the offending discharge to be mucus only. It is significant to note that in 6 other cases, given oral doses of stilbestrol varying from 0.1 to 1.0 mg.

therefore the prognosis is not as favorable. It does not respond as well to radiation, so that an operation is most important.

In our series, 11 were classified as adenoacanthoma of which 3 survived five years or longer.

#### SYMPTOMS

Metrorrhagia, spotting, or a blood-tinged watery malodorous discharge is the predominant symptom, as it occurs in 95 per cent of the cases.

Postmenopausal bleeding, especially after a year, is always important as, with a normal cervix, two-thirds of the cases are of malignant origin.

Pain is usually absent except in the late stages and is an index of extension of the disease.

#### DIAGNOSIS

Microscopic examination of the growth is essential for diagnosis, thus a curettage is necessary to procure the tissue.

John Clark has pointed out that the passage of a uterine sound produces profuse bleeding, which would be absent in normal cases.

The method developed by Papanicolaou in his work at the Woman's and New York Hospitals for the diagnosis of carcinoma of the uterus by a study of the vaginal smears may be of value, if it proves to be accurate in early cases, but it requires the services of a trained cytologist to correctly interpret the findings. A recent report by Papanicolaou and Traut<sup>3</sup> described the method is of great interest.

#### PROGNOSIS

The Grades I and II, adenoma malignum type, give a high percentage of cures if treated in the early stages of the disease. In Grades III and IV the prognosis is more grave, depending upon the duration and extent of the growth.

The prognosis is contingent upon an early diagnosis and a prompt and adequate treatment. The time lost before the patient seeks relief for the irregular bleeding or discharge has been estimated to average between seven and eleven months. Valuable time is often wasted in patients with bleeding associated with fibroids due to an incomplete diagnosis of a co-existing carcinoma of the corpus uteri.

As an aid to prognosis, Healy has suggested dividing the cases into clinical groups according to the extent of the disease as shown by the increased size of the uterus.

Group I, The uterus is normal in size, with a depth of 3 inches. Has the most favorable prognosis.

Group II, A moderately enlarged uterus, 4½-inch depth, size of two and one-half month pregnancy. Intermediate as to hope of cure.

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## THE DIAGNOSIS AND TREATMENT OF CARCINOMA OF THE CORPUS UTERI BASED ON EXPERIENCES AT THE WOMAN'S HOSPITAL\*

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A PRESENTATION of the results of handling a large group of cases in a single institution in accordance with accepted methods of treatment, together with a careful follow-up study, is of value and importance. A comparison with the results of other operators in the same field adds to the interest of such a presentation.

The series at the Woman's Hospital includes 192 cases of corpus carcinoma observed during the period from 1919 to 1941 inclusive.

### CLASSIFICATION

We follow the classification proposed by Ewing, who divides endometrial cancer histologically into four grades:

- Grade I: Superficial papillary adenoma malignum
- Grade II: Adenoma malignum
- Grade III: Adenocarcinoma
- Grade IV: Diffuse anaplastic carcinoma

Grade I is of low malignancy, while Grade IV is very malignant, anaplastic, and consequently radiosensitive.

Usually cancer of the corpus tends to produce the type of cell from which it arises, hence columnar epithelium and gland formation result, while the type of cell in cancer of the cervix is usually of the squamous variety. Occasionally corpus carcinoma may be composed of both cylindrical and squamous epithelium, and it is then designated as adenoacanthoma. This type is rare and metastases are more frequent,

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Crossen<sup>9</sup> has devised an ingenious method of placing the capsules and holding them in the required position by means of wires. His article should be consulted for the details of the technique.

These methods all require accurate measurements of the size and shape of the uterine cavity. Heyman stresses the great caution necessary in applying his method, and states that perforation of the uterus is unavoidable in a number of cases. To avoid difficulty in removing the capsules he places a glass drain in the cervix to prevent contraction. He gives two treatments, averaging 1,500 mg. hours each, given three weeks apart. He does a hysterectomy only if symptoms reappear.

At the Woman's Hospital in every case of potential carcinoma of the corpus, a careful preoperative study of the patient is made, which includes a urologic and proctoscopic examination, blood study, and, in marked anemia or cachexia, a transfusion may be given. A diagnostic curettage is done under anesthesia. Care is taken to curette systematically and with gentleness the anterior and posterior wall and the cornua. Two 50 mg. capsules of radium element in tandem formation with 1 mm. of platinum and rubber screening are inserted to the fundus and anchored by suture through the cervix and vulva, a self-retaining catheter is inserted to keep the bladder empty, and the curettings are sent to the laboratory for a six-hour report (paraffin section). If the diagnosis is "benign," the radium is left in place for a period in accordance with the requirements of the case. If "malignant," a dosage of 2,400 to 4,000 mg. hours is given. A complete hysterectomy and bilateral salpingo-oophorectomy are done in from four to six weeks later.

In certain cases when the patient is not cooperative, we may do the hysterectomy earlier than four weeks after radiation. We have not encountered any unusual difficulty by so doing.

After convalescence is established, the patient receives a series of deep x-ray therapy by the Coutard technique.

I do not believe it wise to give preliminary x-ray therapy by the fractional method before the hysterectomy on account of the loss of valuable time, except in cases where the disease has extended outside the uterus and a hysterectomy is not feasible. Such a course would take a month and, with the delay associated with the intracavitary radiation, the hysterectomy would be delayed for over two months. Prompt surgery is the essential treatment and is vitally important.

In the technique of hysterectomy, the cervix should be closed by suture, both tubes should be clamped on opening the abdomen, and clamps placed down each broad ligament to prevent dispersal of carcinoma cells as a result of the manipulation. The technique of Worrall<sup>12</sup> and Lahey,<sup>13</sup> or that of Richardson<sup>14</sup> or Farrar<sup>15</sup> is most efficient for a safe operation and for giving adequate support for the upper pelvic floor.

Group III, A markedly enlarged uterus 5 inches or more in depth, size of three month pregnancy. Is much less favorable for a cure.  
 Group IV, Extension of disease beyond the uterus. Is the least favorable type.

The statistics of Healy, Norman Miller, and others show generally a better prognosis in small- or normal-sized uteri.

#### TREATMENT

The ideal treatment for corpus carcinoma is a prompt total hysterectomy with salpingo-oophorectomy, performed with a technique that insures prevention of spill or spreading of the cancer cells during the manipulation. As a preliminary diagnostic curettage is nearly always necessary, intracavitary radiation should be done at the same sitting to render the tumor cells inactive.

The hysterectomy should be done usually in from four to six weeks subsequently, after all reaction from the irradiation has subsided. After convalescence from the operation, deep x-ray therapy by the fractional method, such as the Coutard technique, should be given.

Unfortunately, as these patients usually are past the menopause age, 50 per cent (53.6 per cent of our cases) are poor operative risks on account of senility, obesity, cardiovascular disease, renal insufficiency, diabetes, or the extent of the disease. Thus irradiation therapy alone must be depended upon in these cases.

In patients with excessive obesity, x-ray therapy is ineffective, as it cannot penetrate sufficiently to deliver the necessary depth dose. In such cases intracavitary radiation is our only resource.

It is technically difficult to introduce radium applicators into the uterine cavity so that the entire area of the endometrium will receive adequate and uniform radiation, especially in a uterus with a large and irregular cavity. Such irradiation is unreliable, as shown by areas of residual carcinoma often seen in the excised uterus. Sackett<sup>10</sup> reports that in our series 1 out of 3 removed uteri showed persistent carcinoma after irradiation. Thus the results with radium alone are much less favorable than when combined with hysterectomy.

Much attention has been given by various workers to devise a satisfactory method of distributing the radium adequately to the entire area of the uterine cavity.

In small- or normal-sized uteri the usual method is to introduce the radium capsules in tandem formation. Owing to the triangular shape of the cavity, this technique may fail to reach the cornua, as capsules in single tandem cannot reach all portions of a Y-shaped cavity if it is enlarged. Schmitz<sup>6</sup> devised a Y-shaped radium container for this purpose.

Heyman<sup>7</sup> packs the uterine cavity with a number of small specially designed radium cylinders until it is filled. This technique requires a large number of small units, which are difficult to apply and to remove.



Heyman's last report in 1941 (cases from 1914 to 1934 inclusive) is as follows:

|   |        |
|---|--------|
| Total cases seen  | 416    |
| Not treated   | 14     |
| Treated radiologically  | 402    |
| Alive five years with no evidence of disease,<br>absolute rate 45.7%, relative rate 47.3% |        |
| Total alive five years (salvage)  | 51.74% |

By Heyman's multiple packing method, used since 1934, he reports a four-year survival of 75 per cent. He appears somewhat reluctant to give up radiation alone, as he advises hysterectomy only after radiation has failed, and wishes to postpone judgment as to the advantages of hysterectomy *versus* radiation alone in frankly suitable operable cases.

Masson and Gregg<sup>16</sup> reported, in 1940, the results from the Mayo Clinic. In twenty-four years, 732 cases were seen and 728 patients were treated with radiation alone; a five-year survival relative rate of 59.5 per cent was obtained. Operation with and without radiation gave a relative rate of 73.1 per cent. Their five-year survival rate of 711 traced patients was 59.8 per cent.

Healy and Brown,<sup>4</sup> in 1939, reported seeing 283 cases in fifteen years, of which 86 were previously treated. Seventy-eight per cent were postmenopausal. One hundred ninety-seven received primary treatment, with a five-year survival of approximately 48 per cent. Ninety-six were treated with radiation alone with a five-year survival of 39 per cent. Ninety-three were treated with radiation and surgery with a five-year survival of 55 per cent. Eight were treated with surgery alone. In a small group of 28 patients treated by their later technique, using 3,000 to 4,000 millicurie hours of radon, they had a survival of 79 per cent. Their average technique comprises curettage, intracavitary radiation of 3,600 millicurie hours, then a deep x-ray series, and six to ten weeks later a complete hysterectomy. His operative mortality was 4.3 per cent.

Norman Miller,<sup>17</sup> in 1940, reported 183 cases seen, 156 treated, 71 by irradiation, 10 by operation, and 75 by irradiation and operation. Of this series, 68 were eligible for a five-year survival study:

|  |       |
|--|-------|
| Irradiation 29 (five-year survival)            | 34.4% |
| Operation 5 (five-year survival)               | 80.0% |
| Irradiation and operation (five-year survival) | 70.5% |
| Absolute five-year survival rate for all       | 52.1% |
| Operative mortality rate                       | 3.5%  |

Miller advocates preliminary deep x-ray therapy before operation.

As a curettage is necessary for a diagnosis in nearly all cases, intracavitary radiation at the same sitting saves precious time, and is I believe of more proved value than x-ray therapy, which should follow hysterectomy.

#### SUMMARY

1. Early diagnosis gives the best chance for a cure.
2. A diagnostic curettage is most important in all cases of persistent bleeding, especially at or after the menopause, to determine the presence of malignancy.

In the inoperable cases, we believe repeated intrauterine radiation is advisable, with a dosage of from 2,400 to 4,000 mg. hours at four-week intervals, depending on the size of the uterus and the result obtained. Whenever feasible, deep x-ray therapy should precede or follow the intracavitary treatment.

Heyman has called attention to the group of cases in which both the cervix and the corpus uteri are involved. He classifies them as "*cancer corporis et colli uteri*."

In my opinion these cases should be treated as cancer of the cervix.

### RESULTS

It is of interest to review for comparison the results recently reported from some of the larger clinics.

An analysis of our results at the Woman's Hospital in cases of corpus carcinoma seen from 1919 to 1935 and followed for five years or longer is presented in Table I. This shows that of a total of 142 seen, 63 survived five years or more, or an absolute rate of 44.4 per cent. Nine were untreated. One hundred thirty-three were treated, with a relative survival of 47.4 per cent. Of those treated by surgery alone there were 27, of whom 17 survived five years, or 63 per cent; by irradiation alone, 69 (operation contraindicated in 37, or 53.6 per cent), 22 survived 5 years, or 32 per cent; by irradiation and surgery 37, 24 survived five years, or 64.9 per cent. Untraced counted as "dead of cancer," 1 case. Two patients refused operation after irradiation. Our primary mortality in operative cases was 3.2 per cent.

TABLE I. FIVE-YEAR END RESULTS, CARCINOMA CORPUS, JAN. 1, 1919, TO DEC. 31, 1935

|   | TOTAL | LIVING<br>5 YEARS | SURVIVAL RATE<br>PER CENT |      |
|---|-------|-------------------|---------------------------|------|
| Total seen  | 142   | 63                | Absolute                  | 44.4 |
| Untreated   | 9     | 0                 | 0                         |      |
| Treated   | 133   | 63                | Relative                  | 47.4 |
| Surgery alone                                       | 27    | 17                | Relative                  | 63.0 |
| Radiation alone*                                    | 69    | 22                | Relative                  | 32.0 |
| Radiation and surgery                               | 37    | 24                | Relative                  | 64.9 |
| Untraced, counted as dead<br>of carcinoma, one case |       |                   |                           |      |

\*Operation contraindicated in 37 (53.6 per cent). Two refused operation after irradiation. In the others, the disease was inoperable.

In my opinion, in view of the more frequent association of carcinoma with fibromyoma (35 to 40 per cent), it is best to remove the entire uterus in all such cases when there is no probability of serious increased risk, and the removed specimen should always be opened at the time of operation unless a carcinoma of the corpus be overlooked.

Complications in the inoperable group, such as pyometra, perforation, and rectal and intestinal stricture are not infrequent.

# CLINICAL, PSYCHIATRIC AND PSYCHOANALYTIC STUDY OF A CASE OF MALE PSEUDOHERMAPHRODITISM

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**T**HIS report deals with a case of male pseudohermaphroditism. In using the term "male pseudohermaphroditism" we are applying the terminology used by Young.<sup>1</sup> By "pseudohermaphroditism" this author refers to a condition in which the sex glands are entirely male or entirely female while the external sex characteristics are partly or wholly those of the opposite sex. "Male pseudohermaphroditism" according to Young is a condition in which the sex glands are male in spite of the presence of many female secondary sexual characteristics.

The present case was studied clinically and the diagnosis was established by laparotomy and by microscopic examination of the biopsy material. Hormonal studies were carried out. The patient was also studied psychiatrically and, in order to obtain more complete data, a psychoanalysis was carried on for six months. Similar cases have been previously reported.<sup>2</sup> To our knowledge this is the first case of verified male pseudohermaphroditism studied psychoanalytically.

## CASE HISTORY

A 17-year-old, white, single patient (S. M., Unit No. 35209) was admitted to the Massachusetts General Hospital complaining of absence of menses and failure of her breasts to develop. The patient had always considered herself a female, physically and mentally healthy, and the equal of companions of her own age. The only abnormalities, in the patient's opinion, were the absence of menses and lack of breast development.

*Summary of History.*—There was no familial history of mental disease or of hermaphroditism. The patient had a normal early development. During childhood she had measles, mumps, chicken pox, and scarlet fever. She had no other serious illnesses or operations. Her mother died following childbirth when the patient was nine years old. During childhood she had been a nail biter, had frequent crying spells, and was easily frightened. There was no history of enuresis or of other neurotic traits. More recently the patient noticed that she had a headache, a lump in the throat and palpitation whenever she was frightened, nervous, or excited. Rare dysuria had been present for three or four years. The patient stated that she had not had any menstrual flow and had noticed the lack of development of breast tissue.

*School History.*—The patient started to school at the age of five and at seventeen she was in the eighth grade. She was kept out of school a great deal because of sickness and frequent change in residence. She was an average student, liked all of the subjects but showed a preference

3. Clinical grouping based on the size of the uterus as an aid to prognosis suggested by Healy is of value; a small- or normal-sized uterus has a better prognosis.

4. The ultimate prognosis depends upon the age, physical state of the patient, duration of symptoms, extent of the disease, a prompt diagnosis, and the type of treatment.

5. A diagnostic curettage and intracavitary radiation, total hysterectomy and bilateral salpingo-oophorectomy, and deep x-ray therapy is the ideal treatment and gives the best results.

6. Total hysterectomy should be the operation of choice in fibroid cases whenever feasible.

7. Operable cases of corpus carcinoma treated by irradiation, surgery, and x-ray should average 70 per cent five-year survival.

8. Inoperable cases with irradiation alone should show an average five-year survival of 35 per cent.

9. In inoperable cases the technique devised by Heyman and that of Crossen hold promise of giving improved results.

10. Irradiation alone has a definite cure value.

11. Each patient with carcinoma of the corpus uteri must be individualized and treated according to the conditions present to obtain the best results.

12. The early prompt removal of the uterus, tubes, and ovaries is the most essential factor in the treatment of carcinoma of the corpus, irradiation being a valuable adjunct.

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*Laboratory Examination.*—Hematologic and urine examinations were within normal limits. Blood Hinton and Wassermann were negative. Phenolsulphonephthalein excretion was within normal limits. Electrocardiogram in recumbent position showed no abnormalities.

*Hormonal and Related Studies.*—Two examinations before operation for the presence of 40 mouse units per 100 c.c. of follicle-stimulating hormone were negative. These assays were carried out on nonconcentrated urine. Two determinations for androgenic substances showed the presence of 28 international units per twenty-four hours.<sup>3</sup> The serum calcium was 9.7 mg./100 c.c. and the total cholesterol was 165 mg./100 c.c. The sugar tolerance curves were within normal limits both before and after the operation. Intravenous pyelogram showed normal size and shape of the kidneys and normal excretion of dye. X-rays after an adrenal air injection showed no evidence of enlargement of adrenals. X-rays of the skull showed no abnormalities.

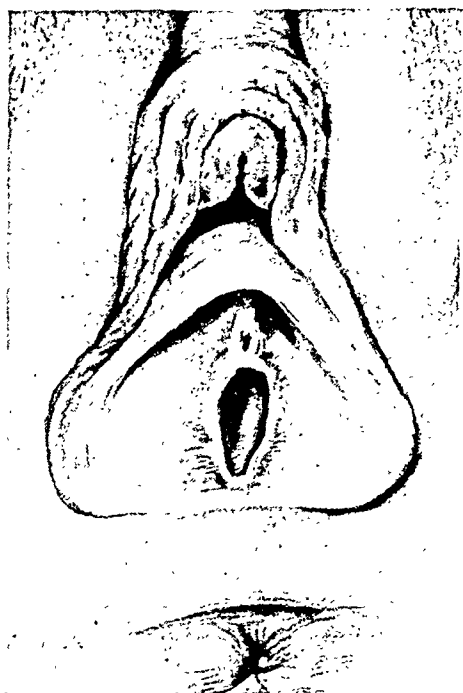


Fig. 1.—The vulva, labia, underdeveloped vagina and the large clitoris.

After the laparotomy, examinations were made for the presence of follicle-stimulating hormone, androgenic and estrogenic substances. Five determinations of follicle-stimulating hormone were made. On Feb. 7, 1938, the test was positive for 66 mouse units per 100 c.c., negative for 100 mouse units per 100 c.c. On Feb. 28, 1938, it was positive for 40 mouse units per 100 c.c. and negative for 67 mouse units per 100 c.c. On March 21, 1938, it was positive for 67 mouse units and negative for 100 mouse units per 100 c.c. These assays were carried out by direct injection of straight urine after acidification with acetic acid to a pH of 5.0 and shaking with ether. Another determination on Dec. 12, 1938, was positive for 20 and negative for 50 mouse units per 100 c.c. The latest determination on Dec. 20.

for drawing. After leaving school she obtained a position as a nursemaid which she held until the present hospital admission.

*Sex History.*—During childhood and adolescence her interests were always feminine. She was interested in dolls, fine dresses, and in playing house. In games she always assumed the feminine role. During puberty she showed interest in boys, went to dances, and here too assumed the conventional feminine role. She became interested in one boy with whom she had some intimate experiences but which never led to attempts at intercourse. Later on she became interested in sewing, cooking, and in housework. In her work as a nursemaid she stated that she enjoyed dressing babies and had typical phantasies of being married and having a family. She preferred little girls to boys, stating that she enjoyed dressing girls in fine clothes. The absence of menstrual periods and the lack of breast development made her feel at times that she could not get married and have children. She could not resign herself to this state of affairs and was in hopes that she could become a normal girl.

*Personality.*—The patient stated that she was usually happy; readily made friends with both sexes. She liked to go out socially, and preferred not to be alone. Her range of interests was limited. She was not religious and had no special hobbies. She read some and stated that she did not like love stories. At times she was not truthful. On the whole she seemed to be an outgoing, dull person, with a moderately low intelligence.

*Physical Examination.*—Physical examination disclosed a young, white adult whose general body contour was that of a thin boy. The shoulders were fairly wide; the thorax was thin; and the pelvis was narrow. The extremities were fairly long with large hands and feet. The hands appeared large boned, the fingers large knuckled and blunt, and the skin was rather coarse and had large pores. There was an acneform eruption over the surface of the arms and upper back. The scalp hair was light brown, straight, and of fine texture. There was a very fine blond mustache; a few hairs were present under the chin but there was no beard. The axillary hair was sparse; pubic hair was female in distribution; there was slight hypertrichosis of the legs. The head showed no gross bony abnormalities. The supraorbital regions were large, and there was a palpable laryngeal prominence. The voice was deep and definitely boyish in quality. The thorax had a shallow anteroposterior diameter and tapered downward with a narrow acute subcostal angle. No mammary tissue was present. Examination of the heart, lungs, and central nervous system revealed no abnormalities. The blood pressure was 140/70.

*Pelvic Examination.*—There was a small mons veneris present. The most striking thing about the examination of the external genitals was the presence of a large clitoris, so large that it could easily be called a small penis (Fig. 1). The measurements were 3 cm. in length and  $\frac{3}{4}$  cm. in diameter. A fairly good prepuce hooded the glans and the structure was more clitorislike than penislike except for its size. Erectile tissue was present in the clitoris. There were good-sized labia majora and small labia minora. The vagina was only a dimple such as is seen in young girls who have no vaginal canal. The urethra was separated from the clitoris or penis and in the usual position of the female urethra. No testicles could be felt in the vulva or in the inguinal canal.

showed a large cavity, much more female than male (Fig. 2). There was no uterus, tubes, or ovaries. No evidence of Müllerian duct formation was present. No prostate or seminal vesicles could be located. Two cords were seen running from the internal ring down behind the peritoneum and ending blindly in the region of the absent prostate. These were taken to be vasa deferentia and were of such good size that it was considered proof that testicles were to be found somewhere. On palpating the inguinal canals with a finger in the abdomen and one on the skin, two testicles were found high in the canals. Incisions were made in the skin over these gonads and they were brought out of their beds. They were normal in every respect: color, size, and consistency. Sections were removed from each for histologic study. The sections were



Fig. 3.—Photomicrograph of nonsperm forming testes. Notice large number of large cells (cells of Leydig) in the supporting connective tissue.

taken from the cortex in the long axis and comprised about one-sixth of the testicular structure. The incisions in the testicles were then closed, and also the skin of the inguinal canals. The abdominal incision was closed in the usual manner.

*Microscopic Examination of Biopsy Material.*—Examination of the removed tissue by the pathologist showed well-formed tubules that were lined by a three to four cell deep layer of epithelial cells completely devoid of mitotic figures (Fig. 3). No spermatozoa were present. Large numbers of polygonal cells of good size were present in the connective tissue septa. These septa were larger and wider than usual. The polygonal cells had eccentric round nuclei and abundant brilliantly acidophilic cytoplasm and were considered to be Leydig cells. These were far more numerous than are seen in a normal testicle. In one area a small collection of cords without lumina was present, suggestive of an undifferentiated stage of testicular development. The testicle was considered to be nonsperm-producing and therefore nonfunctioning as far

1938, was positive for 30 mouse units and negative for 50 mouse units per 100 c.c. The last two assays were carried out by precipitation and concentration on follicle-stimulating hormone by the tannic acid procedure. The recovery of follicle-stimulating hormone was not complete and the lower values are probably due to the incomplete recovery. These studies show that there was an increased excretion of follicle-stimulating hormone following the operation. The quantity of this hormone excreted is in excess of what one would expect to find in an individual with active gonads secreting adequate androgen or estrogen. The amount of follicle-stimulating hormone secreted by this patient is of the range usually found in castrates and in individuals during and after menopause. After the operation one determination showed the presence of 120 mg. of C17 ketosteroids (method of Callow).

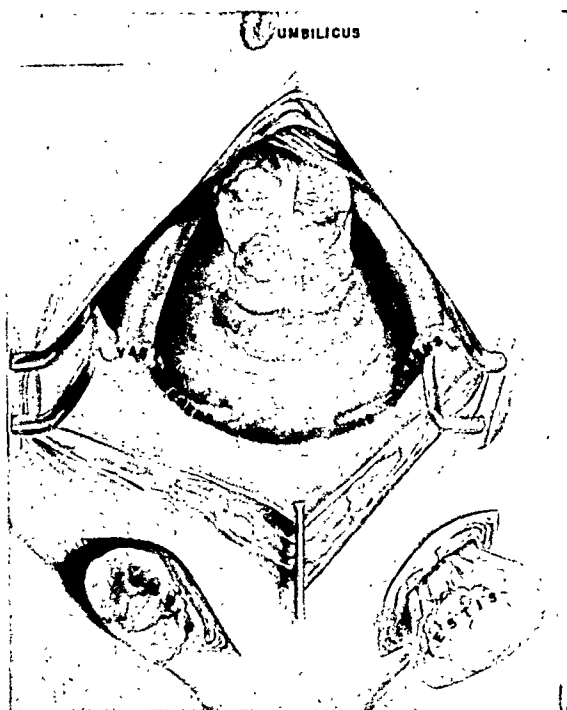


Fig. 2.—The female type of pelvis as seen at laparotomy, showing absence of all female pelvic organs.

*Mental Status.*—The patient was slovenly in appearance, her hair was stringy and disorderly; her complexion was poor. She used lipstick and red fingernail polish. She smiled rather easily, occasionally in a silly, sly fashion but never inappropriately. The patient seemed very shy and not at all talkative. There was no abnormality of mood and no evidence of hallucinations, delusions, or paranoid ideas. The patient was well oriented for time, place, and person. Her memory was good in all modalities and her grasp of information was below normal. The I.Q. was 74.

*Operation.*—A laparotomy was performed on May 29, 1937. The liver, spleen, and gall bladder were normal. The kidneys were both present and of normal size and in the normal position. The appendix was found in its proper position and was removed. Inspection of the pelvis



follicle-stimulating hormone greater than 40 mouse units per 100 c.c. of urine while those after operation did, is not quite clear. It is possible that the preoperative urines were more dilute. The 17-ketosteroid excretion was within normal limits and requires no comment. The androgens as determined by biologic assays were slightly low; whether this is the usual finding in cryptorchidism the authors do not know.

From the behavior point of view this individual with predominately masculine structure and the above hormonal picture was reared as a female, had feminine interests, and passed as a female. The psychoanalytic study indicated the patient's early emotional development was typical of that found in females.

We believe that this study offers presumptive evidence that the eventual development of the female did not at all go hand in hand or correlate with the structural and glandular picture. The presumption is that factors other than the anatomic and glandular ones played the predominating role in the emotional and psychosexual development. What these other factors are is at present not clear. However, it is of interest and significance that this status can exist in an individual. This study would indicate that broadly speaking the environmental and situational factors (reared as a girl, identification with mother, relationship to father, etc.) in this patient played the predominating role in her psychosexual and emotional development.

During the operative procedure it was decided that the testicles should not be removed. It was felt that the excision of the testes might bring about a sudden cessation of hormones and might bring about a "menopause" with its attending symptoms. The testes were left in as androgenic hormone produced by them should prevent castration symptoms. It was decided eventually to give the patient large doses of estrogenic substances to stimulate breast development and later to attempt a plastic operation for the formation of a vagina.

#### SUMMARY

A case of pseudohermaphroditism was studied clinically, psychiatrically, psychoanalytically and from the hormonal point of view. Structurally the patient was preponderately a male with nonsperm-producing testes. The hormonal studies showed an increased urinary excretion of follicle-stimulating hormone after laparotomy and biopsy of the testes. This increased excretion of follicle-stimulating hormone was not present before operation. The urinary androgens were well within the normal range for males and females. The psychiatric and psychoanalytic studies indicated that the patient had an emotional and psychosexual development typical for females.

The authors wish to express their thanks to Dr. Fuller Albright for his critical evaluation of the endocrine findings and also to Dr. R. I. Dorfman, Yale University School of Medicine, New Haven, Conn., for his determination of androgenic substances.

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as spermatozoa were concerned. However, the large number of interstitial or Leydig cells suggested active function on the part of the organ secreting androgens.

*Summary of Psychoanalysis.*—The earliest memory which the patient recalled was an episode at the age of four in which she was taking the female role while playing with dolls. Her earliest impression of her father dealt with ideas of her father's cruelty and her mother's drudgery. The patient identified herself with the mother. Later material indicated a shift in her attitude to one of rivalry with the mother. The death of the mother in childbirth when the patient was nine years old emphasized the cruelty and dread of the father and led to the idea that the father would beat and maltreat the patient just as he had her mother. It seemed that from this point in her life she remained identified with her mother, and developed anxiety in relation to her father. There were several anxiety dreams which the patient had dealing with fear of her employer and fear of operations. These dreams associated directly to memories of scenes in which the patient felt that her father would injure her just as he had beaten the mother.

Later phantasies indicated that she had transferred her fears to other men, and the idea she clung to even up to the present was that men are cruel, unreliable, and are not to be trusted. There was a great deal of introspection as to what role the father could have played in the death of the mother, and she attempted during early adolescence to find out details of the mother's death, and of the place where her mother was buried. Her lack of menses emphasized her inferiority. This material was invariably associated with ideas of being injured.

Her interests in clothes and in men became more marked during adolescence. With considerable difficulty she described her conflict in relation to men. Eventually she described her overt sex activities with her "boy friend" and indulged in masturbation with typically feminine masturbation phantasies. These concerned her friend and later concerned the analyst.

In brief, the psychoanalytic material concerning her emotional development and phantasy life was quite typical of that found in females. The details of the psychoanalytic material will be reported elsewhere.

#### COMMENT

Our studies on this patient indicated that from the anatomic point of view we were dealing with a person having preponderately masculine characteristics (presence of hirsutism, shape and contour of the body, presence of rudimentary penis, presence of nonsperm-producing undescended testes, absence of breast development and absence of uterus, tubes, and ovaries). The female structures present were labia majora and minora, female type of urethra and a rudimentary vagina. From the hormonal point of view the preoperative studies indicated a normal absence of an increased excretion of follicle-stimulating hormone.

From an endocrine point of view this patient is apparently a normal male except for cryptorchidism. Because of nondescent of the gonads, spermatogenesis has been interfered with, since for the completion of spermatogenesis a temperature lower than that of the body is necessary. The high excretion of follicle-stimulating hormone in the urine is an expected finding in cryptorchidism.<sup>4</sup> Just why the two follicle-stimulating hormone tests before operation did not show excretions of

she had received intermittent treatment in the Vanderbilt Clinic for three and one-half years, for her rectal stricture, with indifferent success. Her symptoms of intermittent rectal bleeding dated back ten years. The rectal canal was 0.4 cm. in diameter. Her past history also included typhoid fever in childhood and an appendectomy with drainage in 1921.

Her ante-partum course was uneventful; the pelvis gynecoid. She was admitted to the labor room two weeks before her expected date of labor, having just ruptured her membranes and having painless contractions. Upon pelvic examination the breech was presenting and a twelve-inch loop of pulsating cord had prolapsed into the vagina. This was replaced under anesthesia and a No. 3 Voorhees bag was inserted into the uterus. The fetal heart remained normal, about 140 per minute for one and one-half hours, following which it became feeble, irregular, and then ceased to be heard so the bag was removed. Desultory pains began on the insertion of the bag and continued somewhat stronger after its removal. She was given an enema at this time, nine hours after admission, with good returns of fecal fluid. Another enema one hour later returned fecal fluid and formed stool. She was delivered, after eight and one-half hours of fair labor, of a stillborn infant by easy assisted breech delivery with slight suprafundal pressure for delivery of the head. Immediately following delivery and for two hours afterward her condition appeared good. Four hours after delivery, however, she began to complain of cramplike abdominal pains which were thought to be afterpains and which were relieved by aspirin and luminol. Her abdomen, however, gradually became more distended and she continued to complain of generalized abdominal pain with increasing abdominal tenderness.

Ten hours after delivery a rectal tube was inserted and a flaxseed poultice was applied with little relief of the distention. Seven hours later she was thought to have early peritonitis and, when the rectal tube was removed, it contained some bloody discharge. An enema was given at this time with no return. One hour later one of the nursing staff noted slight cyanosis of the patient's lips but was not alarmed and did not call the house physician until her pulse became feeble and later imperceptible. She did not rally and was pronounced dead twenty-one hours after delivery. Permission for autopsy was obtained.

#### EXTRACT FROM AUTOPSY RECORD (NO. 13,623)\*

About 1,500 cm. of thin, cloudy, blood-tinged fluid with flecks of fibrin was present in the abdominal cavity. The gastrointestinal tract was tremendously distended with gas. The transverse colon and the splenic flexure were filled with a hard firm mass of feces. The peritoneal surfaces of the pelvic viscera were covered with a fibrinopurulent exudate. The uterus was enlarged and reached up out of the pelvis. Several small myomas of the uterus were present. There was nowhere any perforation of the genital organs.

The rectum had been completely separated into two pieces, 2 cm. below the proximal end of a stricture, which, 10 cm. in length, affected the terminal part of the rectum. The proximal end of the rupture of the rectum was separated by about 10 cm. from the distal end. The rupture was an intraperitoneal one (Fig. 1).

\*The autopsy was performed by Dr. Robert C. Horn of the Department of Pathology.

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## DEATH DUE TO INTRAPERITONEAL RUPTURE OF A STRICTURED LYMPHOGRANULOMATOUS RECTUM DURING PARTURITION

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**F**ORTUNATELY, there is a high degree of sterility in women suffering from lymphopathia venereum. This disease, especially in its late stages with rectal stricture, is a serious complication of pregnancy and causes the obstetrician grave concern in his choice of method for delivery. A narrowed rectal canal which is just adequate in the non-pregnancy state, may become almost occluded with the edema which occurs due to increased venous and lymph stasis of the pelvic viscera during pregnancy. Dilatation of the colon with varying degrees of debilitating colitis often results. Added to this is the trauma to the rigid rectal wall in delivery via the vaginal route and a stormy puerperium with severe, almost intractable, distention may be expected. Even cesarean section does not always obviate severe distention and a stormy convalescence.

In the Sloane Hospital for Women on the obstetric service there have been 7 proved cases of lymphopathia venereum in the past four years. During this time there were 6,497 births. Of these 7 cases, 3 were delivered of premature 7½ months' babies spontaneously; 1 at full term spontaneously; 2 by cesarean section, one of which also had a permanent colostomy done at the same time. One of the section cases had had a severe bout of debilitating colitis in her seventh month, which fortunately yielded to conservative therapy and her puerperium was uncomplicated. One case terminated fatally for mother and infant and will be reported in detail. (One case of pregnancy with rectal stricture due to lymphopathia venereum further complicated by fibroids was terminated in the fourth month by hysterectomy and is not included in this group.)

### CASE REPORT

J. T., 32-year-old negro housewife, grav. ii, para i, whose only child, born seven years previously, died at the age of three months, cause unknown, had registered in Sloane antepartum clinic well in the third month of her present pregnancy and had insisted on continuing it despite her being advised against doing so. She had had a positive Frei test in October, 1937, at which time the Wassermann was negative, and

Seven centimeters above the stricture of the rectum, the sigmoid colon showed a sharp narrowing of the lumen, over a distance of 3.5 cm. Just above this stricture a wide-mouthed false diverticulum 7.5 cm. deep had been formed. The sigmoid colon showed extraordinary dilatation and thinning of the wall (Fig. 2).

The strictured portion of the rectum had an internal circumference of about 2 cm. The constriction at the point of the rupture was slightly more marked than elsewhere.

A bolus of feces was impacted in the sigmoid immediately above the stricture of the rectum. An extremely large mass of feces in the sigmoid colon proximal to the second stricture was present. The internal circumference of this stricture was 2.5 cm.

The epithelium of the distal part of the rectal stricture appeared gray, glistening, and thick, above this, granular.

The edges of the tear were rounded and covered with pink and gray granulations. There were also a few areas of hemorrhage. The muscularis was thick and firm. A disproportionally large mass of rather firm adipose tissue with streaks of fibrous tissue surrounded this portion of the rectum.

The mucous membrane of the strictured sigmoid colon was granular. The muscle was thickened and fibrin was present in the surrounding fat tissue.

#### HISTOPATHOLOGY

*Rectum.*—The microscopic findings were characteristic for lymphogranulomatosis with stricture of the rectum: cell infiltrations, especially of eosinophiles and plasma cells, in the mucosa, submucosa and muscularis, also in the walls of the vessels; thickening of the connective tissue and of the muscularis; necrosis of the cell infiltrations, thickening of the subperitoneal fat tissue; dilatation of the lymphatics and narrowing of the smaller and greater vessels by thickening of their intima and media.

The mucosal epithelium was either squamous or atrophic or ulcerated.

Peculiarities of the autopsy findings were the extensive local changes of the vessels in a person only 32 years old, without any alterations of the coronary arteries and with only slight thickening of the aortic intima.

Fibrosis of the muscularis mucosa and rupture of the elastic tissue of the vessels and between the muscle tissue were striking.

At the point of rupture of the rectum, the atrophy of the mucosa, which was replaced by connective tissue and hemorrhages, was extreme.

A striking finding was a hemorrhage from a thrombosed vessel far from the site of the rectal rupture.

Worth mentioning also was the bacterial invasion of the wall and of the interior of the vessels of the wall at the edge of the rupture.

Interesting renal lesions interpreted as lymphogranulomatous were present. Small interstitial groups of plasma cells were seen. In one area densely infiltrated by lymphocytes and plasma cells, a group of convoluted tubules were distended with granular debris in which nuclear fragments were present. The cellular infiltrate formed a suggestive papillar projection into one of these tubules (Fig. 3).

#### DISCUSSION

According to Yeomans,<sup>1</sup> rupture of the rectum may be the result of trauma or occur spontaneously. Impalement, bullet wounds, perforation

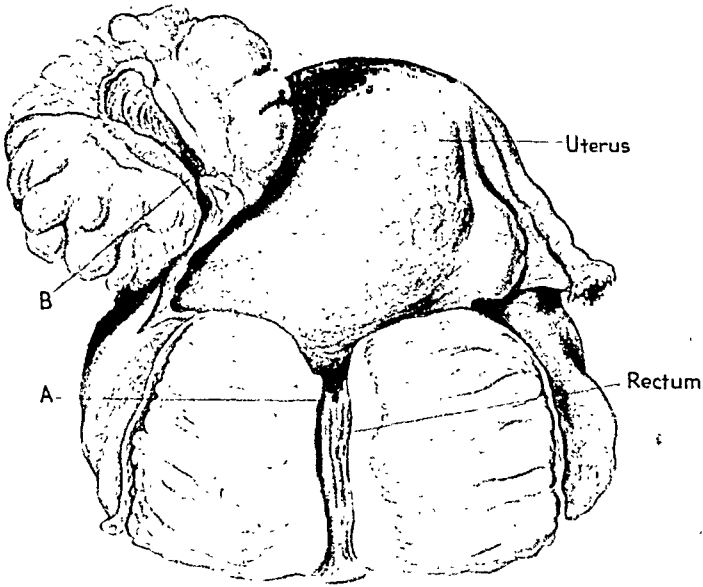


Fig. 1.—Rupture of rectum due to lymphogranuloma venereum.

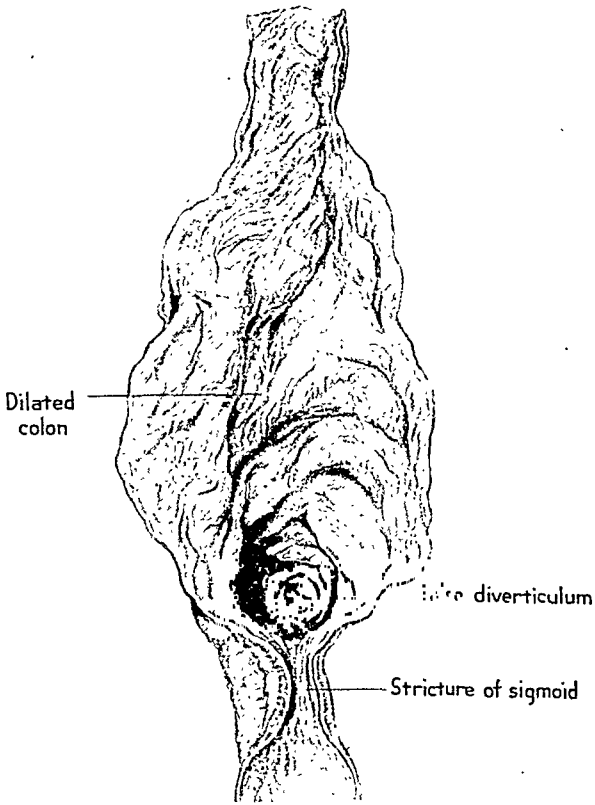


Fig. 2.—Stricture of sigmoid colon with a diverticulum above.

Traumatic rupture of the diseased rectum (for example during dilatation of a stricture) is of more frequent occurrence.

Warthen<sup>7</sup> and Bacon<sup>8</sup> cautioned against even digital exploration in such cases. Warthen combined colostomy with obliteration of the "cul-de-sac" to avoid the danger of dilatation.

Lichtenstein<sup>9</sup> published 5 cases of rectal stricture observed at autopsy. The cause of death in Case 3 was peritonitis, probably due to spontaneous perforation of the sigmoid with ileosigmoidal fistula (Fig. 4); in Case 4 a chronic ulcerated granulomatous proctitis with marked stenosis, decubital ulcers of the sigmoid with perforation and diffuse fecal peritonitis.

The case of Dorsett<sup>16</sup> and the case of Kassebohm and Schreiber<sup>10</sup> are the only two cases in the literature of rupture of a stricture of the rectum occurring at delivery. These strictures were probably due to syphilis. The case of Kassebohm and Schreiber<sup>10</sup> was complicated by a rectovaginal fistula. Our case is the first proved case of spontaneous rupture of lymphogranulomatous stricture of the rectum at delivery. The diagnosis "lymphogranuloma venereum of the rectum" has been established during life by a positive Frei test four years ago, by an elevated blood globulin, by biopsy of the strictured rectal tissue taken one year ago, which showed a lesion compatible with lymphogranuloma venereum and by the autopsy findings. What are the causes of this rupture? It seems probable that the strictures of the rectum and the sigmoid raised the interior pressure of the bowel because the upper part of the sigmoid must strain to expel the contents of the bowel. The extraordinary dilatation and thinning of the wall of the upper sigmoid favor this interpretation. The raised interior pressure caused the rupture, because the wall of the bowel was abnormal.

The contracting uterus may have tugged on the rectal wall. The expelling pains may have pressed the breech presentation against the most vulnerable portion of the wall of the rectum. This pressure may have been much raised because the room of the pelvis was already considerably narrowed by the extensive development of inflammatory tissue in the wall of the rectum.

Another question is, why is the rupture transverse and not longitudinal?

The rectum is a cylinder and its normal wall may have a uniform thickness. The strains or tensions by the interior pressure are doubly as great in the longitudinal direction as in the transverse one. We should then have expected a longitudinal rupture. Tensions of the wall may be raised by holes, notches, and sudden change in the direction of the wall. The ulcerated part of the wall could correspond to such holes and notches. Weakening of the wall and reduction of the elasticity could have furthered such a transverse rupture.

There has been found a bacterial invasion of the wall of the ruptured rectum. Whether the infection preceded or followed the rupture cannot be stated.

An interesting finding is rupture of a thrombosed vessel in the wall of the rectum, far from the site of the rectal tear. We raise, but cannot answer, the question whether this hemorrhage had anything to do with the origin of the rupture of the rectum.

by bougies, enema tubes of the sigmoidoscope are such traumatic causes, as well as contusions by a kick or fall or other indirect violence.

Spontaneous ruptures may also be caused by sudden increase of intra-abdominal pressure as from violent vomiting, lifting heavy weights or severe straining at stool.

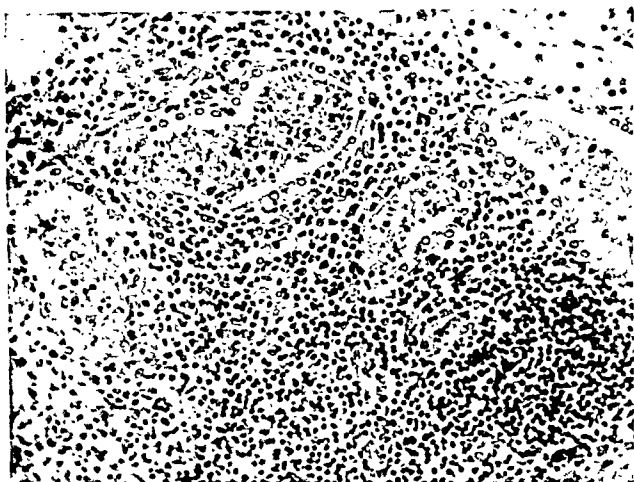


Fig. 3.—Kidney, rounded cell infiltration in cortex.



Fig. 4.—Shows a strikingly similar lymphogranulomatous stricture of the rectum with an ileosigmoidal fistula. The cause of death was peritonitis, probably due to perforation of sigmoid. (Case reported by Dr. L. Lichtenstein.)

Cases of spontaneous rupture of the healthy rectum have been reported by Heineke,<sup>2</sup> Christian,<sup>3</sup> Delbet,<sup>4</sup> Bunge,<sup>5</sup> and Burkhardt.<sup>6</sup> Burkhardt's patient was saved by an early laparotomy.



danger should indicate the advisability of early radical surgical treatment before pregnancy or in the earliest months of pregnancy. Furthermore, in the case of collapse or beginning peritonitis, during and after delivery of a patient with lymphogranulomatous rectal stricture, it is of greatest importance to suspect a rupture of the strictured rectum. Then surgical help would be immediate.

We wish to acknowledge our indebtedness to Drs. Kesten, Sproul and Horn for their friendly collaboration and to Dr. L. Lichtenstein for the permission to reproduce the photograph of his case (Fig. 4).

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## ENDOMETRIAL CYST OF THE GROIN ASSOCIATED WITH A DECIDUAL REACTION IN THE APPENDIX

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THE occurrence of aberrant endometrial tissue in the groin was first described by Cullen<sup>1</sup> in 1896 and since that time a number of cases have appeared in the literature. The condition, however, is rare. In Counseller's<sup>2</sup> large series of 884 patients with endometriosis, no case was observed with endometrial involvement of the inguinal region and Polster, as cited by Hosoi<sup>3</sup> in a series of over 1,000 collected cases of endometriosis, discovered only 34 with involvement of the inguinal region. The total number reported at the present time is probably less than 50.

Much of the discussion in the reported cases has been devoted to the pathogenesis of the lesion. Five possibilities have been advanced to explain the occurrence of ectopic endometrium in the groin: (1) Implantation (applicable only to those cases associated with an inguinal hernia or a patent canal of Nuck); (2) direct extension along the round ligament from a neighboring process within the pelvis; (3) origin from cell rests of Müllerian origin; (4) metaplasia of "multipotent" serosal epithelium; (5) metastasis by way of the blood or lymph channels. Many of the cases reported in the literature were associated with hernial

That pregnancies may be successfully completed even in the presence of a lymphogranulomatous stricture of the rectum is shown by the cases cited above from the Sloane Hospital and by the following cases: Huet and Villars<sup>11</sup> have reported a case in which proctitis developed after pregnancy, necessitating a colostomy; lesions persisted during two succeeding pregnancies, terminating in complete stricture of the rectum. The Frei reaction was positive. The severe disease of the rectum did not cause any obstetric difficulty or hazard. Fagarasanu<sup>12</sup> has performed an intrasphinctereal and abdominoperineal resection of the rectum for stenosis in the second month of pregnancy. It was followed by the normal development of pregnancy and satisfactory results one year later.

Two particular features in the pathology of this case remain to be discussed:

1. The multiple type of the rectal stricture.
2. The lymphogranulomatous focus in the kidney.

1. Bacon is of the opinion that rectal strictures seldom extend above the level of the third sacral vertebra (posterior leaflet of peritoneum) and are usually single. Mathewson<sup>13</sup> found three types of stricture: (A) An annular stricture 1 to 6 cm. above the anocutaneous margin. This type is usually single, may be multiple. (B) A barrel-shaped stricture from 2 to 6 cm. long with smallest aperture proximally, distally ulcerated. (C) Diffuse involvement of the whole bowel distal to the pelvicrectal junction.

Taylor<sup>14</sup> described a high stricture in the descending colon and another lower stricture in the rectum, in a patient with a positive Frei test. In both, the lumen was narrowed and the mucosa showed generalized ulceration. The cul-de-sac was normal. Our case is quite similar to his.

2. Interesting renal lesions in our case were interpreted as lymphogranulomatous. Reichle and Connor<sup>15</sup> first described follicular granulomatous lesions in the kidneys. The infiltration was in part in the glomeruli, but chiefly in the interstitium, and in places led to the formation of small abscesses. We have in our records another case (Autopsy No. 11,631) in which renal lesions, interpreted as lymphogranulomatous, were present. There was a positive Frei test.

*Pathology of Fetus.*—No lymphogranulomatous lesions were found, but merely early maceration with congestion and hemorrhages into the viscera.

#### SUMMARY

1. This is the first proved case of spontaneous rupture of a lymphogranulomatous stricture of the rectum at delivery.

2. It is possible, though it cannot be proved in our case, that the rupture was initiated by spontaneous hemorrhage in the wall of the rectum.

3. We believe that the pressure from within had much to do with the origin of the rupture.

4. The case is exceptional in that there were two strictures in the bowel, one in the rectum, and the other in the sigmoid; the lymphogranulomatous changes were more severe in the rectum than in the sigmoid.

5. We come to the conclusion that pregnancy and delivery increase the danger of rupture of a lymphogranulomatous rectal stricture. This

pedicle. Upon sectioning this presented the characteristic firm, white, whorled appearance of fibromyoma. Two smaller subserous myomas were present and the uterine wall contained many more. The appendix measured 6 cm. in length and no gross abnormality was noticed other than congestion of the serosal vessels.

The inguinal tumor was oval in shape and measured 6 by 4 by 3 cm. The external surface was smooth and bluish white in color. Upon opening, a single thin-walled cyst was disclosed, filled with serosanguinous fluid and lined by a smooth, shining fibrous membrane. At one pole an irregular mass of fat was present which was partially incorporated within the wall.

Microscopic examination of the uterine curettings revealed masses of decidual cells and chorionic villi covered by both syncytial and Langhans' cells, the normal histologic appearance of placental tissue in the



Fig. 1.—Photomicrograph showing decidual reaction in the wall of the appendix.  
X260.

first trimester. Deep within the wall of the uterus were several islands of endometrium, consisting of glands surrounded by the usual stroma. Oddly enough, only a slight and certainly very patchy decidual reaction could be found in the stroma of the "adenomyomas" and several of them presented no sign of this change.

Two small cysts were present in the mesoappendix which were lined by flat epithelium and, just beneath the serosa, there were several small groups of decidual cells (Fig. 1). There was no histologic evidence of an inflammatory process.

Sections taken through the wall of the inguinal tumor revealed a striking picture. An epithelial lining was present which varied in nature from place to place. In some fields it was flattened, almost nonexistent, and in others it was tall columnar in type and invaginated, forming cryptlike spaces. Endometrium-like stroma, considerably distorted by hemorrhage, was present beneath the epithelium and scat-

sacs, and in these the implantation theory of origin has been most forcibly championed. In others the process was thought to have reached the groin by direct extension along the round ligament.

The following case is of interest, especially from a standpoint of pathogenesis, since no hernial sac existed and no pelvic peritoneal endometriosis was found at operation:

Mrs. H., Caucasian, was first seen in January, 1940, at which time the following notation was made upon her Clinic record:

"Aged 38. Hypertension for years. One sister has hypertension and nephritis. One child 17 years old. Menses regular. Two therapeutic abortions in 1936 and 1937. Now wants children. Has lump in the right groin the size of a hen's egg, 17 years' duration. This varies in size and is painful at times. It is above Poupart's ligament, not reducible, soft to palpation and there is no impulse on coughing. B.P. 160/90. Pelvic examination negative. Heart normal. Diagnosis: Essential hypertension, and hydrocele of the canal of Nuck. Patient advised against pregnancy and operation urged for removal of the inguinal tumor."

The patient decided against operation and was not seen until eighteen months later, at which time she returned after having missed one menstrual period. Pelvic examination revealed the uterus slightly enlarged, the cervix soft and a hard, freely movable mass the size of a handball in the right adnexal region. The breasts were slightly enlarged and the Friedman test was positive. The inguinal tumor was larger and was causing more discomfort.

The past history of Mrs. H. was carefully investigated. She was now 39 years old, had one child, aged 18 years, and two therapeutic abortions had been performed when she was several weeks pregnant, one in 1936 and the other in 1937, because of essential hypertension and chronic interstitial nephritis. For several years her blood pressure had been high, usually over 170 systolic and 120 diastolic, and the urine always contained albumin and casts. One sister has hypertension and nearly died in eclamptic convulsions during her only pregnancy six years before.

A diagnosis of pregnancy complicated by essential hypertension and fibroids of the uterus was made and therapeutic abortion, followed by pelvic laparotomy and removal of the inguinal mass, was advised and consented to. These procedures were carried out under cyclopropane anesthesia, on July 8, 1941, at her seventh week of pregnancy.

The diagnosis of pregnancy was substantiated by the uterine scrapings. At laparotomy, multiple fibroids were found, one pedunculated, the size of a baseball, in the right adnexal region. Both tubes and ovaries were normal in appearance. A subtotal hysterectomy was performed and the appendix removed. After closing the abdomen, the cystic tumor in the right inguinal region was dissected out and removed intact. It was not associated with a hernial sac. The patient's post-operative course was uneventful and she left the hospital in good condition. Follow-up examination six weeks after the operation showed her to be symptom free and in good health aside from the pre-existing hypertension.

*Pathologic Examination.*—The uterus revealed a large tumor mass, 5 cm. in diameter, arising from the right side of the fundus by a narrow

invaginations are quite typical, and there are areas of stromal tissue including scattered patchy nodules of definite decidual cells. . . .

"The appendix likewise shows a number of small areas of decidual reaction, although there are no endometrial glands to be found. The two cystic spaces lined by very flat epithelium impress me as being peritoneal invaginations such as one not infrequently finds on many of the pelvic organs. It would hardly seem justifiable, on the basis of the section sent, to designate the appendiceal involvement as an endometriosis, especially in view of the fact that perfectly normal appendices are encountered which show a typical decidual reaction. Such cases are instances of the ectopic decida which may be found, not only on the appendix, but on the back of the uterus, in the ovaries and elsewhere. They appear to indicate that vestigial patches persist in various parts of the pelvis which retain a sensitivity to the pregnancy hormone, but in view of the complete absence of epithelium and glands they can hardly be spoken of as areas of endometrium."

*Pathologic Diagnosis.*—(1) Pregnancy, first trimester; (2) multiple myomas of the uterus; (3) adenomyosis, uterus; (4) endometrial cyst of the groin; (5) ectopic decidual reaction, appendix; and (6) serosal inclusion cysts, appendix.

#### COMMENT

In considering the pathogenesis of the aberrant endometrium in this case, it is obvious that the lesion could not have resulted from direct implantation, since no communication existed between the peritoneal cavity and the groin; it is equally obvious that direct extension can be discarded as a source of origin since no sign of pelvic endometriosis was observed at operation. The endometrium, then, either must have reached the inguinal region through the blood or lymph channels or must have developed in situ by metaplasia of embryologically "multipotent" serosal epithelium.

There is considerable evidence at hand indicating that bits of endometrium may at times, although surely very rarely, gain access to blood or lymph vessels and produce distant lesions. Viable endometrium has been found in the pelvic lymph nodes on numerous occasions and cases of endometrium in the brachioradialis muscle and thigh have recently been reported (Navratil and Mankin). Hobbs and Bortnick<sup>5</sup> have succeeded in producing viable endometrial growths in the lungs of rabbits by injection of homologous endometrium, emulsified with normal saline, into the venous system. However, the generally sharp limitation of aberrant endometrial growths to the lower abdomen and contiguous structures indicates that the metastatic method of origin must apply only to exceptional cases.

In the present case it is suggested that the ectopic decidual reaction in the appendix, indicating an abnormal response to the hormones of pregnancy, is presumptive evidence that the full-fledged endometrial cyst of the inguinal region arose by metaplasia of bits of embryologically predisposed serosal epithelium, perhaps due to a different type of hormonal stimulation.

Normally, the endometrial stroma in the uterus responds to progesterone by a decidual reaction which becomes most marked just before menstruation. During pregnancy this change is tremendously accentuated.

tered here and there were sharply outlined nodules of unmistakable decidual cells (Figs. 2 and 3). The presence of large pigment-filled macrophages completed the picture, and there was no hesitation in classifying the tumor as an aberrant endometrial cyst.

The ectopic decidual reaction in the appendix and the presence of epithelial-lined cysts seemed to indicate that the latter, also, might be of endometrial origin, although the epithelium was not typical and no



Fig. 2.—Wall of the inguinal cyst showing a flat epithelial lining and nodules of sharply circumscribed decidual cells bulging into the lumen of a crypt.  $\times 260$ .

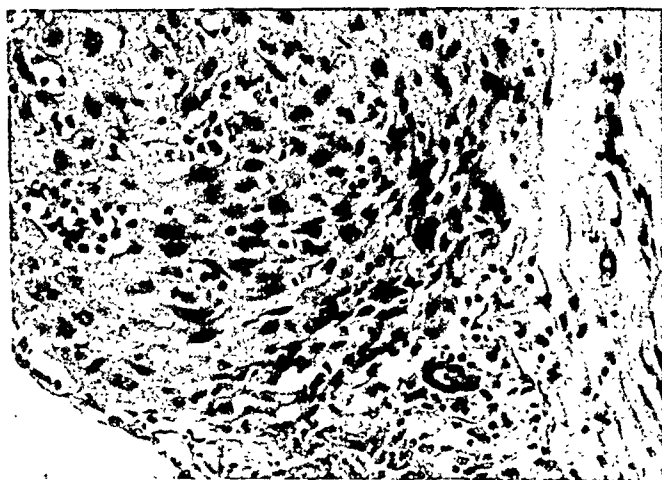


Fig. 3.—A mass of decidual cells in the wall of the inguinal tumor.  $\times 580$ .

stroma, other than the decidual cells themselves, could be found. Novak<sup>4</sup> said, after reviewing a section of the appendix and the inguinal tumor: "The tumor of the inguinal canal shows what I think is undoubtedly endometrium in its wall. Such aberrant endometrium does not always show a typical stromal mantle, but the epithelium and the gland

literature. One of the few cases reported is that of Reis and Sinykin<sup>6</sup> who described the occurrence of ectopic decidua in an appendix removed from a woman four months pregnant.

In view of the fact that bits of tissue remote from the endometrium have the ability to react in this manner to the hormonal stimulation of pregnancy, an intrinsic property of endometrial stroma itself, it is certainly reasonable to assume that such bits of tissue may, under a different type of hormonal stimulation, produce full-fledged endometriomas. The simultaneous occurrence of an ectopic decidual reaction in the appendix and an endometrial cyst of the groin in the present case lends support to this suggestion.

Witherspoon<sup>7</sup> has pointed out the frequent association of hyperplasia of the endometrium, myomas of the uterus and endometriosis and has advanced the hypothesis that all of these states are ultimately due to the same factor, the estrogenic principle from the ovary. This hypothesis is supported by a large amount of clinical and pathologic data, explains the frequent simultaneous development of the three conditions, and does not necessarily invalidate the implantation theory since some factor must determine and regulate the successful implantation and subsequent development of these hormone-labile bits of tissue.

#### SUMMARY

A case of endometrial cyst of the groin associated with a decidual reaction in the appendix is presented. The pathogenesis of the lesion is considered, and it is suggested that the aberrant endometrium in the groin arose by metaplasia of "multipotent" serosal epithelium. The absence of a hernial sac and associated pelvic peritoneal endometriosis, and the simultaneous occurrence of ectopic decidua in the appendix lend support to this suggestion.

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The author defines efficient reproduction as making each pregnancy count with resulting normal infants with the potentialities of normal adult life, at the same time with least maternal morbidity or mortality. The grande multipara does not do a very efficient job according to recent studies (Eastman, Yerushalmy and Kramer). National health demands spacing of pregnancies and forbearance on the part of the ill, dysgenic, and grande multipara. A woman should have her first baby after twenty and before twenty-five, and should end her childbearing career at 35.

R. J. WEISSMAN.

ated and the endometrium, at least the outer two-thirds, becomes converted into a mass of decidual cells. This hormonal "responsiveness," however, varies in different portions of the endometrium and generally decreases as the basal layer is approached. This feature is well illustrated in sections taken through the walls of pregnant uteri; the extreme basal portion of the endometrium takes little part in the formation of decidua.

A decidual reaction also occurs, under the influence of pregnancy, in the stroma of endometrial growths remote from the uterus, and it is likewise often "patchy" in nature. One of us (I. L. T.) has recently observed a case of widespread pelvic endometriosis at cesarean section in which the redundant hemorrhagic growths on the uterus, tubes, and ovaries clinically simulated an infiltrating malignant neoplasm; the question was settled by microscopic examination which revealed an extreme decidual reaction, masses of sharply outlined decidual cells compressing and surrounding relatively few dilated endometrial glands.



Fig. 4.—A group of decidual cells in the tip of a mucosal fold of a tube removed at a post-partum sterilization.  $\times 260$ .

In this particular case the stroma cells of the ectopic endometrial growths were unusually sensitive to the pregnancy hormones. In other cases of endometriosis, this sensitivity, as evidenced by the formation of a decidual reaction, varies greatly from place to place, or may be missing entirely. In the case reported here, only a slight decidual reaction could be found in the stroma of the aberrant endometrium within the wall of the uterus, while a marked, although "patchy," reaction was present in the wall of the inguinal tumor.

Ectopic decidual reactions may occur alone in the complete absence of endometrial glands; we have seen a number in the walls and mucosal folds of tubes removed at post-partum sterilizations. One case presented a mass of sharply outlined decidual cells in the tip of a mucosal fold (Fig. 4) and careful microscopic search of the entire segment of tube removed at the operation failed to disclose endometrial glands. That such ectopic decidual reactions are not uncommon is conceded by many pathologists; yet there has been little mention of the condition in the



the perineal nerves of both legs. There was no edema. The patient complained of exquisite tenderness in both lower extremities.

The tendon reflexes of both upper extremities were hypoactive, but equal. In the lower extremities all reflexes were absent. There was no muscular wasting and no fibrillary twitching.

Red blood cell count was 3,000,000, and hemoglobin 50 per cent. The patient was given a transfusion of 450 c.c. of whole blood. She was given one ampoule of ergometrine and 6 tablets of ergotrate gr.  $\frac{1}{320}$  in a period of twenty-four hours. On admission she was given 2 Gm. of sulfathiazole and 1 Gm. every four hours; also 50 mg. of thiamine chloride and 50 mg. of nicotinic acid daily.

On the following day, January 13, temperature was 100.6° F.; pulse, 106; and she was irrational. The red cell count was 3,350,000; white cell count, 7,800; and hemoglobin, 56 per cent. An additional transfusion of



Fig. 1.—Lower extremities of the patient on the fifth hospital day.

400 c.c. was given, which was followed by a chill and elevation of temperature to 106.6° F., which dropped to 100° twelve hours later. The discoloration of the lower extremities was increased in intensity and the patient complained of inability to move her legs. Dorsalis pedis pulsations could be felt. Sedimentation rate was 125 mm. in one hour; bleeding time, eight minutes; and platelet count, 205,000.

On January 14, temperature was 100° F., and pulse, 110. The patient was not quite as irrational and her general condition seemed improved. There seemed to be a coalescing of the discolored areas which extended to the middle of both legs. The feet felt cold and dorsalis pedis pulsations were not felt, while those of the posterior tibials were questionable. The legs were elevated and hot water bottles applied.

On January 15, temperature was 100.6° F., and pulse, 120. The patient seemed rational and responded to questions intelligently. Lochia

## BILATERAL DRY GANGRENE OF BOTH LOWER EXTREMITIES DUE TO ERGOT

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IT HAS been found from a review of the literature that peripheral gangrene is a rare complication of ergot administration. The following case is presented to emphasize the fact that serious complications from ergot do occur. Patients receiving the drug should be observed carefully for toxic manifestations and should not be given the drug indiscriminately.

### CASE REPORT

Mrs. H. G., white female, aged 42 years, gravida viii, para v, was admitted to Grady Hospital on Jan. 12, 1942. Her chief complaint was pain in the lower abdomen, passage of large clots of blood from uterus, and pain in both legs.

The patient stated that her last normal menstrual period was on July 20, 1941. She was apparently having a normal gestation until Jan. 7, 1942. At this time without apparent reason she began to have cramplike pains in her lower abdomen, which were associated with uterine hemorrhage. A private physician was called and later the same night she passed a four and one-half months' fetus. The doctor administered fluid extract of ergot and told her to take one-half teaspoonful every four hours. On the following morning she began to complain of some tingling sensation throughout both lower extremities. She continued to bleed and have cramplike pains throughout that day and again called her physician. He applied hot packs to the extremities and advised her to continue taking one-half teaspoonful of fluid extract of ergot every four hours. She continued to bleed for two days and was seen again by her physician and told to continue the treatment. She bled for two more days and the cramplike pains throughout her abdomen were still present. On the fourth night she became irrational after having two chills followed by high fever. She was brought to the emergency clinic on Jan. 12, 1942. The total intake of ergot at home was two fluid ounces.

The patient had had 7 confinements and was always attended by a midwife, never receiving medication for post-partum bleeding.

On the day of admission, Jan. 12, 1942, the patient was apparently in shock, having lost a considerable amount of blood; pulse was 128, blood pressure, 70/?; and temperature, 101° F. The abdomen was essentially negative and was not tender. Examination revealed the cervix to be soft and about 3 cm. dilated. A piece of placental tissue about 5 cm. long was in the external os and was removed with a sponge forceps. Adnexa were essentially negative.

The anterior aspects of both lower extremities were extremely purple with discoloration which resembled erythema ab igne. Both dorsalis pedis and posterior tibial pulsations were present and the legs and feet were warm. There was marked muscle tenderness along the course of

## PATHOLOGIC FINDINGS

The upper half of the leg was normal in appearance. At the mid-portion of the leg there was an irregular line of transition from a normal appearance to a bluish gray discoloration. This discoloration continued down over the dorsum and sides and posterior portion of the foot, until it reached about 1 cm. proximal to the roots of the toes, and 1 cm. superior to the sole of the foot. Another line of demarcation which was fairly sharp was at a point where the skin and underlying soft tissues had been much shrunk, and had the appearance of mummification. As the foot was held up to the light these mummified parts were translucent. The skin and subcutaneous tissues underlying the grayish blue discoloration were very edematous and had a slightly hemorrhagic appearance.



Fig. 3.—Section through a vessel and nerve showing premortem clot, intimal changes and toxic changes in the nerve bundles ( $\times 30$ ).

As the gastrocnemius muscle was dissected, scattered areas of extravasated blood were noted. As the vessels and nerves of the leg were dissected there were noted in the arteries fairly firm thrombi which had the appearance of being premortem. Otherwise there was no recognizable gross pathology of the vessels and nerves.

A section through the skin and subcutaneous tissue taken from the lower third of the right leg revealed hyperkeratoses of the epidermis and necroses of the epithelial cells. The corium was markedly edematous and fragmented. In the subcutaneous tissue there was a vessel, apparently a vein, whose wall was markedly edematous and fragmented, and whose lumen contained a post-mortem clot. A section through the muscle tissues of the leg revealed the sarcolemma to have completely disappeared in some areas. In others it was present but was rather widely separated from the muscle fibers. The muscle fibers had lost

was slight, and there was no tenderness in the course of the femoral veins. The legs now presented a typical picture of dry gangrene. Posterior tibials and dorsalis pedis pulsations were absent, and there was beginning demarcation in the middle third of the leg. Kahn report at this time was negative. A light tent was ordered and surgical consultation requested. That night a bilateral sympathetic bloc using 1 per cent novocain was done. No improvement was noted.

On January 16, the temperature was 99.8° F. and pulse 90. The patient seemed generally better. The toes at this time were mummified and the feet were plantar flexed. The femoral pulsations as well as the popliteals were good. Sulfathiazole was reduced to 1 Gm. every six hours. Blood cultures during all this time were negative.

On January 17, the patient was given 500 c.c. of blood and transferred to the surgical service.



Fig. 2.—Section through a blood vessel showing premortem clot and changes in the intima ( $\times 30$ ).

Temperature and pulse remained normal, and on January 21 the line of demarcation had become well established at the middle of the upper third of the leg. The left leg was amputated under sodium pentothal anesthesia. The patient stood the operation well and was given 250 c.c. of plasma postoperatively and 250 c.c. of whole blood the following day. Postoperative course was uneventful.

Four days later, January 25, the right leg was amputated, the patient having received several preoperative transfusions of whole blood and plasma.

Remainder of the postoperative course was uneventful and the patient was dismissed from the hospital on February 5, her twenty-fifth hospital day.

From the history of this case and the pathologic findings which were presented it is assumed that this is one of ergot gangrene.

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## BILATERAL OVARIAN CARCINOMA ASSOCIATED WITH INTRAUTERINE PREGNANCY

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OVARIAN neoplasms associated with pregnancy occur infrequently. The incidence usually quoted is 0.1 per cent or less. There are only a few reports of malignant new growths combined with pregnancy. In those which have been reviewed, malignant disease was found in from 5 to 7 per cent of the pregnancies complicated by ovarian tumors.

We were able to collect a total of 14 cases, including the present report, of malignant ovarian disease with pregnancy. Szathmáry, in 1933, reported 3 cases of his own which are included in our group. This author, also, brought out the fact that he had found 39 additional cases in the literature. Of the 39, 7 had sarcomas and the rest carcinomas. These cases were not described in any detail. In our group, 5 had sarcomas and the remainder carcinomas. The case of Hempel which was reviewed could well have been a Krukenberg type of new growth because there were bilateral ovarian tumors which were secondary to a carcinoma of the stomach. There may well be some question as to the diagnosis of sarcoma which was made in certain of the cases, if one considered the present-day concept of the pathology of the ovarian neoplasms. Table I briefly outlines the cases which we found in the literature.

The cases of Kosmak and Traut and Kuder are the only ones that were found in the American literature. Therefore, we regard it to be of sufficient rarity and interest to report ours.

T. B., a 42-year-old, white married woman, was admitted to the Cincinnati General Hospital, No. 165203, for the first time, Oct. 28, 1941. Six months prior to her admission, the patient had been aware of a gradual increase in the size of the lower abdomen along with a dull, aching pain in the right lower portion most of the time. Upon arising, Oct. 26, 1941, the pain suddenly became severe and cramp-like. It continued so until the morning of the date of hospitalization, at which time it became most intense. There was neither nausea nor vomiting. The appetite had been poor since the onset of the acute pain. The last bowel

their nuclei, but the striations were quite definite. Between the muscle fibers, there was a sparse infiltration of polymorphonuclear neutrophiles. Another section was through nerves, arteries, and veins. The arteries showed what was apparently some medial thickening and slight reduplication of the internal elastic lamina. Many of the veins contained premortem thrombi, some of which showed very early organization. The walls of the veins were infiltrated with small round cells and plasma cells, particularly the outer part of the media and adventitia. There was some fibroblastic activity in the media. Most of the nerve bundles showed marked degeneration. The connective tissue binding the arteries, nerves, and veins together showed a rather marked fibroblastic reaction, was very vascular, and was densely infiltrated with small round cells, plasma cells, and a few polymorphonuclear neutrophiles. A section taken at the junction of the mummified skin of the foot and the adjacent skin revealed both surfaces to be covered with hyperkeratotic degenerating stratified squamous epithelium. In the underlying corium,\* however, there was a sharp line of demarcation between the two areas. The corium of the mummified part was dense, acellular, and hyaline, while the adjacent tissue was edematous and fragmented.

#### COMMENT

The toxic manifestations of ergot may take two different forms: One affects the central nervous system and is characterized by headache, vertigo, nausea, and frequently convulsive seizures, thirst, and confusion. This may be followed by depression and syncope, which may cause death. The other form is characterized by lowering of blood pressure, parathesias, anesthetics, muscular pains, and cyanoses of the extremities, particularly the digits. The latter may rapidly assume the dry form of gangrene.

The pathogenesis of gangrene in ergot intoxication has been demonstrated to be a primary vascular spasm followed by thrombosis due to stasis and injury to the intima. The pathologic picture of ergot gangrene is usually one that shows marked proliferation of the intima, thrombus formation in the vessels, thrombophlebitis and ischemic changes in the nerves.

Toxic effects usually follow the administration of the drug over a long period of time. There is evidence that some patients may have an idiosyncrasy to the drug, as shown by a report where one drachm of the fluid extract caused symptoms. Gangrene and death have occurred after taking 12 gr. of the extract.

While it is possible that this woman had an idiosyncrasy to the drug, her condition was unquestionably due to overdosage.

It is to be remembered that the patient first complained of tingling in the lower extremities following the administration of the fourth dose of one-half drachm of the fluid extract. However, it must also be remembered that over a relatively short period of time she received two ounces of the fluid extract equivalent to 960 gr. plus six  $1/320$  gr. tablets of ergotrate plus 1 ampoule of ergometrine. This is well over the toxic dose. Therefore it is gathered from the above facts that a large dose of the drug with the possibility of a slight sensitivity resulted in marked vascular disturbance of the lower extremities. This in time caused a complete bilateral symmetrical dry gangrene.

movement occurred following an enema two days before admission. There were no urinary tract symptoms.

Menstruation began at the age of 13 years, recurring regularly every twenty-eight to thirty days. The periods were usually of three days' duration, but in recent years nine days. The flow was never heavy. A slight vaginal discharge was present for several months. The last period occurred Aug. 29, 1941, and the previous menstrual period was Aug. 1, 1941.

The patient had been married twenty-three years. There had been 6 full-term uncomplicated deliveries and 2 miscarriages. The last term pregnancy occurred twelve years ago. All of the children were well. Her past health had been good until two years ago. During this time there were intermittent aching pain in the right lower abdomen and throbbing headaches in the right frontal and occasionally, in the right temporal areas, dizziness and some blurring of vision.

On physical examination, the temperature was 97° F., the pulse rate 92 per minute, the respiratory rate 20 per minute, and the blood pressure 175 systolic over 110 diastolic. She appeared moderately acutely ill. There was slight dehydration. The color was good. The head and neck were normal except that the upper teeth were absent, the lower ones were carious, and the thyroid contained a small nodule. The lungs and heart were normal. The breasts were negative and no enlarged lymph glands were palpable.

The abdomen was rounded, extended slightly above the level of the costal margin, and moved with respirations. The right lower quadrant was more prominent than the remainder of the abdomen. The liver and spleen were not felt. A definite cystic, tender mass which extended to the umbilicus was lying in the right lower quadrant. A questionable smaller mass was found in the left lower quadrant. There was no costo-vertebral angle tenderness. Peristalsis was good.

Vaginal examination revealed normal external genitals. The urethra was healthy. There was no infection of Skene's or Bartholin's glands. The perineum was lacerated and a moderate sized rectocele was present. The anterior vaginal wall was slightly relaxed. Although the vaginal mucosa appeared healthy, a moderate amount of greenish yellow, somewhat foamy discharge existed in the vagina. The cervix was soft and its surface was rough as a result of several small lacerations. The uterus was difficult to outline, but it was felt to be anterior and to the left. The size was normal. A large, cystic tender mass arose from the right appendages and extended into the abdomen as described. A smaller cystic nontender mass involved the left ovary. Rectal examination was negative. The remainder of the examination was not unusual.

Our impression was that the patient had bilateral ovarian cysts with probable torsion of the pedicle or intracapsular hemorrhage of the right tumor.

The laboratory findings were as follows: The urine was negative; hemoglobin, 14 Gm.; white blood cell count, 9,050; and Wassermann reaction, negative.

The following notation was made by Dr. V. Bradley Roberts at the time of the pelvic examination under ether anesthesia, Oct. 29, 1941: "An intrauterine pregnancy is very likely. The larger of the two tumors is on the left side and the smaller one on the right."

The operative note as of the same date reads as follows: "Immediately upon opening the abdomen a large amount of blood-tinged

TABLE I. SUMMARY OF REPORTED CASES

| AUTHOR                                 | TYPE OF TUMOR   | PERIOD OF PREGNANCY TUMOR WAS FOUND | TREATMENT OF TUMOR                      | TERMINATION OF PREGNANCY        | RESULT                        |
|--|---|-------------------------------------|---|---------------------------------|-------------------------------|
| Swan in 1897 quoted Spiegelberg (1867) | the following 3 authors and their cases:                            |                                     |   |                                 |                               |
|  | Myxosarcoma, bilateral  | Post partum                         | None                                    | Spontaneous delivery            | Died ninth day                |
| Hempel (1875)                          | Carcinoma, bilateral and secondary to gastric carcinoma             | Post partum                         | None                                    | Spontaneous delivery            | Died twenty-eighth day        |
| Ruge (1886)                            | Myxosarcoma, bilateral  | Sixth month                         | No further details given                |                                 |                               |
| Zieckel (1907)                         | Adenocarcinoma, unilateral  | Seventh to eighth month             | Removed                                 | Spontaneous delivery eighth day | Died 3 months; carcinomatosis |
| Kosmak (1914)                          | Adenocarcinoma, unilateral  | "Early"                             | Removed                                 | Aborted on fourth day           | Well                          |
| Szathmáry (1933)                       | Small round cell carcinoma, unilateral                              | 4½ months                           | Removed                                 | Spontaneous delivery            | Well                          |
|  | Round cell carcinoma, unilateral with extensive pelvic tuberculosis | Post partum, first day              | Complete removal                        | Spontaneous delivery            | Well                          |
|  | Spindle cell sarcoma, unilateral                                    | 2½ months                           | Removed                                 | Spontaneous delivery at term    | Well                          |
| Trillat and Puthod (1934)              | Atypical epithelial carcinoma, unilateral                           | Term                                | Removed at time of section              | Cesarean section                | Not mentioned                 |
|  | Lymphosarcoma, unilateral   | "Early"                             | No further details were given           |                                 |                               |
|  | Papillary cyst Adenocarcinoma                                       | Post partum, eleventh day           | Removed                                 | Spontaneous delivery            | Died                          |
| Traut and Kuder (1940)                 | Papillary cyst, adenocarcinoma                                      | No details were given               |   |                                 |                               |
|  | Adenocarcinoma  | Fourth month                        | Complete removal                        | Removed at operation            | Well                          |
| BoSSERT* (1942)                        | Papillary serous cyst adenocarcinoma, bilateral                     | Second to third month               | Complete removal and deep x-ray therapy | Removed at operation            | Well after 3 months           |

\*Case reported in the present paper.



ovary was involved in a soft semisolid tumor which measured 12 by 6 by 4 cm. The surface was smooth except for one small, slightly elevated, firm, yellow area. The content was brainlike in character and had the same dark color as the surface.



Fig. 2.—Microphotograph of the left ovarian tumor.

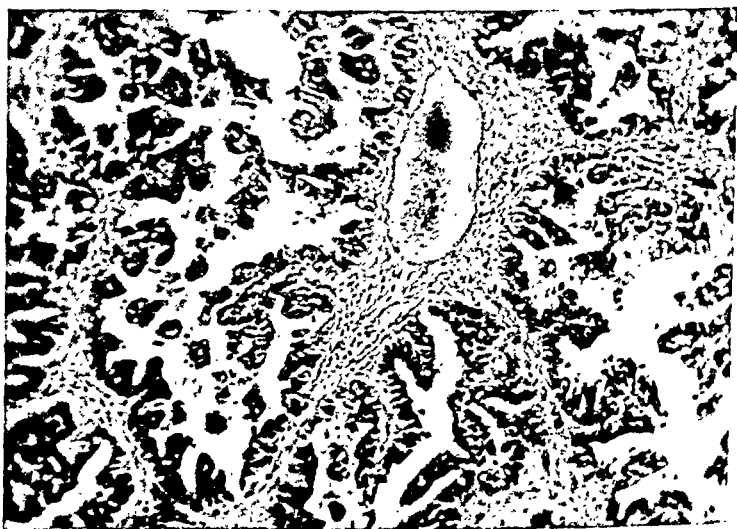


Fig. 3.—Microphotograph of the right ovarian tumor.

*Microscopic.*—The left tumor (Fig. 2) was predominantly papillary. The capsule was composed of dense fibrous tissue. Its thickness was decreased in some places due to the encroachment of the epithelial elements of the tumor. The connective tissue stroma was scant in amount. The papillas were lined by 2 to 3 layers of epithelial cells. The latter were both polygonal and columnar in form. The taller cells were greater in number. The nuclei were large and almost filled the entire cell. They

fluid without odor escaped. On the right side was a dark, semi-solid tumor about the size of an adult fist, one surface of which was adherent in the pelvis. The tumor had a strangulated appearance. On the left side was a ruptured large cyst approximately the size of an adult head. The uterus was soft and enlarged to about the size of a ten weeks' pregnancy. Metastatic implants were present on the left broad ligament as well as on the bladder peritoneum. There were no mesenteric nodes, no nodules in the peritoneum, and no metastatic involvement of the liver."

Supravaginal hysterectomy and bilateral salpingo-oophorectomy were done. The small implants were removed with the specimen.

The patient withstood the operation well. Her course was afebrile and the wound healed by primary union. The patient complained that the throbbing headache noted in the past history was more intense. A thorough neurologic investigation revealed no definite cause for this complaint. Roentgenograms of the skull, chest, and pelvis showed no metastatic involvement. Deep x-ray therapy was started on the seventeenth postoperative day and the patient was discharged on the twenty-first day.

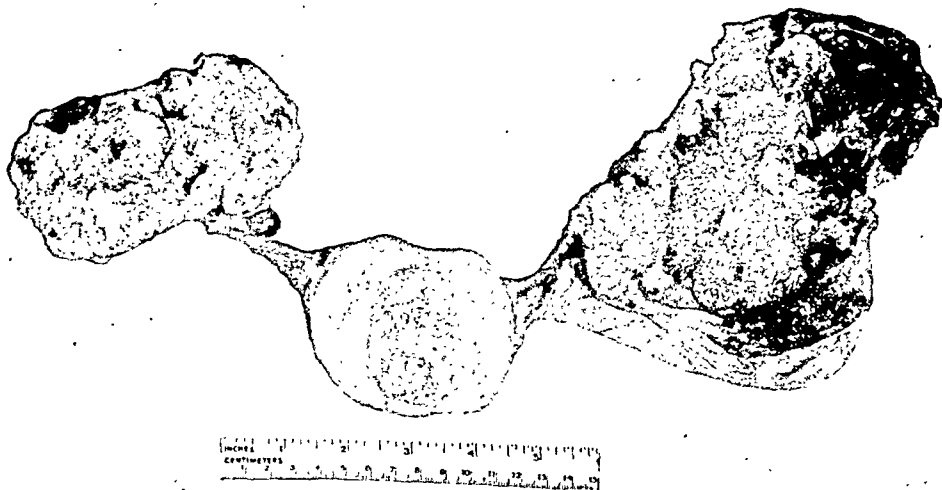


Fig. 1.—Sagittal section of the uterus and the tumors.

After three months, the patient has remained well. During this period of time 13,000 r. units of deep x-ray therapy through 6 portals have been given.

The pathologic description of the specimen is as follows:

*Gross.*—The specimen consisted of the uterus, tubes, and ovarian tumors (Fig. 1). The dark red and softened uterus was symmetrically enlarged to twice its normal size. Anterior median section revealed a pregnancy. The placenta was implanted on the posterior wall. Upon opening the amniotic sac, a 2.5 cm. fetus was recovered. The tubes were normal in all respects. The left ovary was replaced by a ruptured cyst, 20 cm. in diameter. The outer surface was glistening and grayish white in color. It was smooth except for one discrete, small, firm papillary projection. The inner surface was completely studded with fused papillary excrescences which were deep red, rough, and firm. The right

## UNILATERAL TWIN ECTOPIC PREGNANCY

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UNILATERAL tubal twin pregnancy is of sufficiently rare occurrence to justify this report.

In 1923 Arey, reviewing all reported cases of twin unilateral ectopic pregnancy, found 38 authentic or positive cases and added 2 of his own. He also found and classified 8 as probable or presumptive and 4 as possible but doubtful cases. Falk and Bliniek in 1938 found 23 additional positive cases published since the work of Arey and added 2 cases of their own to make a total of 65 authentic reported cases. Christitch added another case. Fishback in 1939 reported a case of simultaneous twin pregnancy in one tube and a single pregnancy in the other tube. Also in 1939 Kaplan reported 2 cases of twin ectopic pregnancy; Reček, of Czechoslovakia, reported a case and recently Fischmann reported a case of interstitial twin pregnancy. To the accepted list of 71 authentic cases, we are reporting an additional one. It might be added, that to our knowledge, this is the first case of its kind at the Cook County Hospital, there having been a total of 903 ectopic pregnancies in the last sixteen years, as far back as we were able to investigate.

M. D., a 30-year-old, colored female, grav. i, para o (having had a spontaneous abortion in 1940), who was separated from her husband eight years previously, entered on the senior author's gynecologic service of the Cook County Hospital, May 20, 1941, with the complaints of abdominal cramps and nausea and vomiting for three weeks. The patient stated that she was perfectly well until three weeks ago, when, after eating breakfast, she became nauseated, vomited, and then experienced "cramps" in the lower abdomen, which were eased by the application of a hot water bag. This syndrome of eating followed by nausea and vomiting with subsequent abdominal cramps and soreness had continued almost daily for three weeks. Her last normal menstrual period occurred March 19, 1941, at which time she flowed for three days, moderate in amount, passed no clots, and had her usual mild abdominal cramps on the first day. The past 2 menstrual periods, which occurred April 19 and May 18, 1941, were characterized by cramping pains in the lower abdomen after spotting for one day on both occasions. Prior to April her menstrual periods had been of the twenty-eight-day type. Three days ago while working she experienced severe pains in the suprapubic area. These lasted about two hours and then subsided upon lying down. The following day on arising from bed she again experienced abdominal pains, this time lasting approximately two and one-half hours. The abdominal pains were described as dull, cramping in character, only at times being sharp and knifelike, which would subside on lying down. The pains usually were in the right lower quadrant and radiated at times to the left lower quadrant. There was no history of fainting.

Physical examination revealed a fairly well-developed, colored female, who appeared to be acutely ill. Temperature was 99.4° F.; pulse, 108;

were hyperchromatic and showed numerous mitotic figures. Nucleoli were occasionally seen. The solid tumor (Fig. 3) was adenomatous and papillary in character. Gland formation was not very distinct. The fibrous tissue capsule was less than 0.5 mm. in thickness. Again, the stroma was scant and delicate. The individual cells were similar to those of the other tumor. In both tumors proliferation and infiltration were evident and there were large areas of necrosis. The solid tumor appeared to have a greater degree of malignancy than the left. The corpus luteum of pregnancy was never satisfactorily demonstrated.

The pathologic diagnosis was serous papillary and adenocarcinoma of the ovaries associated with an early pregnancy in the uterus.

#### DISCUSSION

Laparotomy is indicated when a proliferating type of ovarian tumor 8 cm. or more in diameter is found in the pregnant woman, because the question of malignancy can never be completely made without it in the majority of cases. If a definite diagnosis of ovarian malignancy is made prior to operation, the indication for the laparotomy should be based upon the extent of the lesion. In the inoperable case, the pregnancy could probably be permitted to go to term. Contrarily, however, in the operable case immediate operation is strongly recommended with no regard to the period of gestation.

Several factors determine the advisability of the removal of the pregnant uterus. The findings at the time of the operation are most important. A distinction should be made between young and old patients, primiparas and multiparas. For example, a complete operation would more likely be done in the woman approaching 40 years of age, who has one or more healthy children than in the younger woman, who is pregnant for the first time.

#### CONCLUSIONS

There are two points which should be emphasized in conclusion:

1. Careful prenatal examination is necessary for the early diagnosis of ovarian tumors in the pregnant woman.
2. Where possible, the nature of the tumor should be well known at the time of laparotomy in order to carry out the proper procedure.

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peritoneum was congested and purplish, and when the latter was incised, there was a slight amount of fresh and old-clotted blood in the peritoneal cavity. The uterus was enlarged to the size of approximately a six to eight weeks' gestation, was soft, hyperemic, and pushed to the left by the right tube which was enlarged and deformed by a soft cystic mass about the size of an orange. The tube was ruptured in the ampullary portion, but the sac was intact. In attempting to deliver the sac, the latter ruptured and two fetuses about the size of an eight weeks' pregnancy were revealed. Since the right ovary was not pathologic, a right salpingectomy was done. Exploration of the left tube and ovary revealed no pathologic findings, and the abdomen was closed. The patient made an uneventful recovery, being discharged from the hospital on the tenth postoperative day.

The following is the pathologic report submitted by Dr. A. B. Ragins of the Department of Surgical Pathology: "Specimen (Fig. 1) consists of a Fallopian tube previously opened and measures 14 cm. in length and 6 cm. in greatest circumference. The external surface is light purplish gray and covered by clotted blood. In the lumen of the tube wall, which is thickened, is a soft papillary structure, resembling placental tissue and 2 fetuses measuring 5.5 cm. (crown-rump). On tracing the umbilical cords to the placenta 2 amniotic cavities were demonstrated, separated by a thin membrane. Gross diagnosis: twin pregnancy of a Fallopian tube. Microscopic: Section of wall of Fallopian tube reveals placental tissue."

#### SUMMARY

We are adding another case of unilateral twin ectopic pregnancy, making a total of 72 reported cases. During the preparation of this report, Dr. F. H. Falls, of the Department of Obstetrics and Gynecology, University of Illinois, notified us by personal communication that he also has a gross specimen of an ectopic twin pregnancy in the ampullary portion of the tube, as yet unpublished.

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respiration, 20; blood pressure, 120/80. The head, neck, heart, and lungs were not pathologic. The breasts were slightly enlarged, the nipples were tender, and a straw-colored secretion was expressed from both nipples. The abdomen was round, firm and elastic. There was definite tenderness in the lower abdomen, more marked in the right lower quadrant, rebound tenderness, and a voluntary muscular rigidity. No mass was palpable nor were the kidneys, liver, or spleen. Pelvic examination revealed a nulliparous introitus, a slight mucopurulent discharge was expressed from the urethra and Skene's ducts, and there were bilateral shotty Bartholin glands. The introitus admitted 2 fingers and the pelvic floor was firm and elastic. The posterior vaginal wall



Fig. 1.

appeared to be raised by a bulging, doughy, tender mass in the cul-de-sac of Douglas. The cervix was soft and smooth, and the os was patulous and pointed down and backward. Attempt at movement of the cervix elicited pain in the lower abdomen, especially in the right lower quadrant. The corpus was not definitely made out due to the extreme tenderness present; however, it was thought to be slightly enlarged, softened, smooth, and pushed toward the left by a tender cystic mass about the size of an orange in the right adnexal area. The left adnexa were tender, but no definite structures were made out. Rectovaginal-abdominal examination confirmed the above, and speculum examination revealed a smooth cervix which took the Schiller stain well. The Falls-Freda skin pregnancy test gave no reaction after thirty and sixty minutes. The hemoglobin was 75 per cent (Tallqvist); red blood count, 3,820,000; white blood count, 9,200; Kahn test, positive; urine, essentially negative. A diagnosis was made of an old-ruptured right ectopic pregnancy with hematocele.

The following day, under nitrous oxide and ether anesthesia, the patient was subjected to a laparotomy. On opening the abdomen, the

ing to Pflueger's glycogen estimation). From this standard solution various dilutions were prepared, and to 1 c.c. of each solution 3 drops of N/10 iodine solution in potassium iodide were added. The same quantity of iodine solution was added to 1 ml. of distilled water, and to this water-iodine solution drops of 20 per cent neutral iron chloride solution were added until the color became identical with that in the glycogen iodine solutions. The results shown in Table I were obtained.

TABLE I

| Concentration of glycogen mg./ml.                          | 1.0 | 0.5 | 0.4 | 0.3 | 0.25 | 0.2 | 0.1 |
|--|-----|-----|-----|-----|------|-----|-----|
| Drops of iron chloride necessary to produce color equality | >15 | >15 | >15 | 5   | 3    | 2   | 1   |

From the above results it can be seen that in the narrow range from 0.25 mg./c.c. to 0.40 mg./c.c., the number of drops of iron chloride required to produce color equality rises from 3 to over 15. Advantage was taken of this fact in the following procedure for estimation of glycogen content in the uterine mucosa.

#### METHOD FOR ESTIMATION OF GLYCOGEN CONTENT IN THE UTERINE MUCOSA

One hundred and twenty-five milligrams of fresh uterine mucosa are digested in a centrifuge tube by adding 0.15 ml. 60 per cent KOH and heating for one hour in a boiling water bath. (If this cannot be done immediately, the mucosa must be kept on ice.) After boiling, 0.3 ml. water and 0.7 ml. 96 per cent alcohol are added and the tube dipped for a short time into the hot water bath. The tube is centrifuged and the supernatant discarded. The precipitate is washed, once with 70 per cent and once with 96 per cent alcohol. The washed precipitate is dissolved in 1 ml. water by warming in a water bath. With this solution the iodine color test was carried out.

Solutions required: (1) N/10 Iodine solution: 25 Gm. of potassium iodide are dissolved in a small quantity of water, 12.7 Gm. iodine are added and when all has dissolved water is added to 1 liter. (2) 20 per cent "neutral" ferric chloride solution: 20 Gm. ferric chloride are dissolved in 100 ml. water and drops of 2N NaOH are added until a permanent precipitate forms. After filtration the solution is ready for use and can be kept in a closed flask for one month.

*Iodine Color Test.*—Add to 1 ml. of the glycogen solution obtained by the above described procedure, 3 drops of the N/10 iodine solution and to a second test tube of the same size 1 ml. water and 3 drops of iodine. Now, add drops of the ferric chloride solution to the water-iodine test tube until color equal to the glycogen iodine is obtained.

*Calculation.*—According to the results obtained with liver glycogen, concentrations of less than 0.25 mg./ml. need less than 3 drops of ferric chloride for color equality. In our procedure, 1 ml. of the glycogen solution corresponds to 125 mg. uterine mucosa, i.e., 0.25 mg./ml. means 0.25 mg./125 mg. uterine mucosa or 0.2 per cent. When 0.3 mg./ml. or approximately 0.25 per cent of mucosa are present, 5 drops are needed and concentrations above 0.4 mg./ml. or 0.32 per cent of uterine mucosa require more than 15 drops. Hence, in order to convert the figures for glycogen concentration from mg./ml. (Table I) into figures of per cent glycogen in the uterine mucosa (Table II), they must be multiplied by 0.8.

# A SIMPLIFIED METHOD OF GLYCOGEN ESTIMATION IN UTERINE MUCOSA FOR CLINICAL PURPOSES

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IN THE cyclic development of the uterine mucosa, two phases are distinguishable: (a) the proliferative phase, brought about by the activity of the follicular hormone and (b) the progestational phase, brought about by the activity of the corpus luteum hormone. In the second phase, anatomic as well as functional changes can be detected: The glands become dilated and coiled and produce mucus and glycogen. Glycogen determinations have been carried out mainly by histochemical methods using Best's glycogen staining. Quantitative glycogen estimations in uterine mucosa have been carried out by van Dyke and Chen<sup>1</sup> in monkeys. Zondek and Stein<sup>2</sup> published quantitative estimations of glycogen with Pflueger's method in human curettage material. They obtained the following results: During the first generative phase (the proliferative phase) human uterine mucosa contained about 0.1 per cent of glycogen in fresh tissue. During the progestational phase the glycogen content rose, the minimum being 0.25 per cent, the maximum 0.66 per cent. In 18.4 per cent of 49 cases of sterility examined, glycogen content in the second phase was much below this minimum of 0.25 per cent although all anatomic changes of the uterine mucosa were normal. This condition of glycogen deficiency has been termed "glycopenia uteri." It was assumed that insufficient glycogen quantities in the uterine mucosa interfere with the imbedding of the fertilized ovum.

Estimation of glycogen in the uterine mucosa of the second generative phase may, thus, serve to determine the cause of sterility, especially in patients with normal menstruation. The purpose of the present paper is to describe a simple method for glycogen estimation suitable for routine tests and not requiring the collaboration of a chemical laboratory. The method elaborated does not yield exact values but is sufficient, from a clinical point of view, to determine whether glycogen is produced in sufficient amounts in the endometrium or not.

Glycogen is generally estimated in laboratories by Pflueger's method: Digestion of the tissue with concentrated potassium-hydroxide, precipitation of the glycogen with alcohol, hydrolysis of the washed glycogen precipitate and sugar estimation in the hydrolyzate. In our method we tried to avoid the last two manipulations, i.e., hydrolysis and sugar estimation. This was done by means of the color reaction of glycogen with iodine.

## EXPERIMENTAL

As no sufficient quantities of uterine mucosa were available, the glycogen-iodine reaction was standardized with crude liver glycogen (purified glycogen was found to be unsuitable).

Crude liver glycogen was prepared by digestion of fresh liver in 60 per cent KOH dilution with 2 volumes of water and precipitation of the glycogen with 4.5 volumes of 96 per cent alcohol. The precipitated glycogen was washed with 70 per cent and 96 per cent alcohol, and a solution was prepared in water containing 1 mg./ml. glycogen (accord-



# A REVIEW OF THE CALDWELL-MOLOY METHOD OF ROENTGEN PELVIC MENSURATION WITH A CORRELATION OF NEW TECHNICAL PROCEDURES

ROBERT TAYLOR, HARTFORD, CONN.

RECENTLY some minor technical changes have been applied to Caldwell and Moloy's method of depicting roentgenographically the osseous structures of the maternal pelvis.

The method described in the literature numerous times consists basically of:

- (a) Stereoroentgenographic examination of the pelvic inlet
- (b) Roentgenographic examination of the pelvic outlet
- (c) Lateral roentgenographic examination of the maternal pelvis with centimeter measurement of the true conjugate

Roentgenographic examination of the maternal pelvis requires first of all accurate posturing of the patient with elimination of roentgenographic distortion in order that interpretation and typing of the pelvis may be made without undue difficulty.

Some means of adjusting the normal plane of the pelvic inlet to have it coincide with the plane of the film is essential for accurate interpretation. Caldwell and Moloy advocated the use of a lumbosacral pad to be placed under the curve of the lumbar spine to adjust, or tilt, the plane of the inlet so that it would be in the identical plane of the film, thereby eliminating distortion in the image. Recently I<sup>3</sup> described an angle block to meet the same requirements as the pad and pointed out some advantages in using the block. A description of this apparatus appears in the reference.

I<sup>4</sup> recently worked out something hitherto untried concerning roentgenography of the inferior pelvic aperture, or pelvic outlet. Working on the theory that stereoroentgenography is superior to single film roentgenography stereoscopic studies were carried out on the pelvic outlet. In this connection it may be pointed out that in orthopedic work stereoroentgenography of the inferior pelvic aperture reveals detail that might remain undisclosed by single film examination. The application of this projection to the pelvic outlet was thought of. In this connection an oblique anteroposterior projection for stereoroentgenography of the inferior pelvic aperture was initiated as follows: With the patient placed in a supine posture on the roentgenographic table, the superior border of the symphysis pubis is oriented on the Potter-Bucky diaphragm so that it coincides with the caudal edge of a 10 by 12 cassette, the short axis of which is in the median plane. The tube is angulated 45 degrees cephalad and the central ray is projected through the localization point (a point 5 cm. caudad to the superior border of the symphysis pubis, Fig. 1) to the film. The roentgen tube is shifted transversely for the stereoroentgenograms.

This is summarized in Table II.

TABLE II

| NUMBER OF DROPS OF FERRIC CHLORIDE REQUIRED | GLYCOGEN CONTENT OF MUCOSA UTERI |
|---|----------------------------------|
| Less than 3 drops                           | Less than 0.20 per cent          |
| 3-5 drops                                   | 0.20-0.24 per cent               |
| 5-15 drops                                  | 0.24-0.32 per cent               |
| More than 15 drops                          | More than 0.32 per cent          |

This technique of assay was now compared with the results obtained with Pflueger's method for glycogen estimation. The results shown in Table III were obtained.

TABLE III. GLYCOGEN CONTENT OF SAMPLES OF MUCOSA TAKEN FROM STERILE WOMEN

| UTERINE MUCOSA NO. | DAY OF CYCLE | DROPS OF $\text{FeCl}_3$ REQUIRED | GLYCOGEN CONTENT ACCORDING TO OUR METHOD | PER CENT GLYCOGEN ACCORDING TO PFLUEGER'S METHOD |
|--------------------|--------------|-----------------------------------|--|--|
| 1                  | 11           | 15                                | 0.24-0.32%                               | 0.26   |
| 2                  | 11           | 15                                | 0.24-0.32%                               | 0.26   |
| 3                  | 12           | 1                                 | less than 0.2%                           | 0.03   |
| 4                  | 12           | 1                                 | less than 0.2%                           | 0.05   |
| 5                  | 17           | 15                                | 0.24-0.32%                               | 0.3  |
| 6                  | 18           | 1                                 | less than 0.2%                           | 0.08   |
| 7                  | 20           | 15                                | 0.24-0.32%                               | 0.27   |
| 8                  | 23           | >15                               | more than 0.32%                          | 0.64   |
| 9                  | 23           | 0                                 | no glycogen detectable                   | 0.03   |
| 10                 | 25           | 15                                | 0.24-0.32%                               | 0.28   |
| 11                 | 25           | 2                                 | less than 0.2%                           | 0.08   |
| 12                 | 25           | >15                               | more than 0.32%                          | 0.38   |
| 13                 | 25           | 4                                 | 0.2-0.24%                                | 0.21   |
| 14                 | 26           | 8                                 | 0.24-0.32%                               | 0.27   |
| 15                 | 26           | < 3                               | appr. 0.2%                               | 0.18   |
| 16                 | 26           | >15                               | more than 0.32%                          | 0.36   |
| 17                 | 26           | >15                               | more than 0.32%                          | 0.40   |
| 18                 | 27           | >15                               | more than 0.32%                          | 0.60   |
| 19                 | 28           | >15                               | more than 0.32%                          | 0.37   |
| 20                 | 28           | >15                               | more than 0.32%                          | 0.37   |

The table shows that information obtained by our simplified glycogen test is in good agreement with that obtained by Pflueger's method. In agreement with the results of Zondek and Stein,<sup>2</sup> 3 cases (Cases 6, 9, and 11) out of 16 cases (Cases 5-20) in the second phase showed glycogen deficiency.

## SUMMARY

A simplified glycogen test for uterine mucosa is described. The test is based on the iodine glycogen color reaction, but does not require the use of a colorimeter. It is sufficiently accurate for detection of sufficiency or insufficiency of glycogen production in the uterine mucosa.

## REFERENCES

1. Van Dyke, H. B., and Chen, G.: *Am. J. Anat.* 58: 473, 1936.
2. Zondek, B., and Stein, L.: *Endocrinology* 27: 395, 1940.

It is not believed that this technique has been described in the literature except in dealing with fractures of the inferior pelvic aperture by the author, and hence has not been universally adopted for roentgenographic examination of the pelvic outlet. No doubt added research will be required prior to evaluating its connection with the pelvic outlet and prior to its adoption by the obstetric and roentgenologic professions. There is the possibility, however, that it may enhance the evaluation of the Caldwell-Moloy method.

So far as concerns the initial description of lateral roentgenography of the maternal pelvis one change was recently made at the Margaret Hague Maternity Hospital<sup>2</sup> by adopting a thin rule of light weight for measurement of the true conjugate, on the roentgenogram. This has recently been described in the literature and attention is again drawn to the reference.

In explanation, the rule consists of a hollow bakelite stem with alternate strips of lead and bakelite, each measuring 1 cm. in length, inserted within the hollow stem. Its extremely light weight prevents its slipping away from its strapping and the centimeter margins are more readily seen on the roentgenogram than was the case with the older brass or steel rules.

It may be seen that minor changes in technique have been made in each of the three types of studies required to complete the Caldwell-Moloy method of pelviroentgenography and no doubt has enhanced the value thereby.

Concerning stereoroentgenography of the pelvic outlet it may be found out later on after more study that this too has added something to the most excellent method first described by Caldwell and Moloy.

#### REFERENCES

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2. Perlberg, H. J.: *Am. J. Roentgenol.* 45: 935, 1941.
3. Taylor, Robert: *AM. J. OBST. & GYNEC.* 43: 140, 1942.
4. Taylor, Robert: *Radiol. & Clin. Photog.* 17: 67, 1941.

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Bunster, E.: *Uterine Intubation*, *Bol. Soc. chilena de obst. y ginec.* 6: 147, 1941.

The author discusses the uses and results with various rubber and metal intra-cervical tubes applied for stimulation of hypoplastic uteri, or in cases of malposition, dysmenorrhea, and sterility. Bunster feels that the mechanical stimulation of the cervix affects pituitary anterior lobe functions. He describes his modification of the Iribarne and Ségond tubes, essentially involving a funneled lower end, whose posterior rim is spout-lipped to lie in close apposition to the seminal pool. A slit in the cervix at 6 o'clock accommodates this portion of the funnel, which is held in place by 5 sutures. The author cites 12 cases in which the tube was used. Dysmenorrhea was relieved in most instances. Enlargement of the uterus and gain in body weight of about 2 kilos was common. Pregnancy occurred in some cases of sterility but the series is too small to evaluate in this respect.

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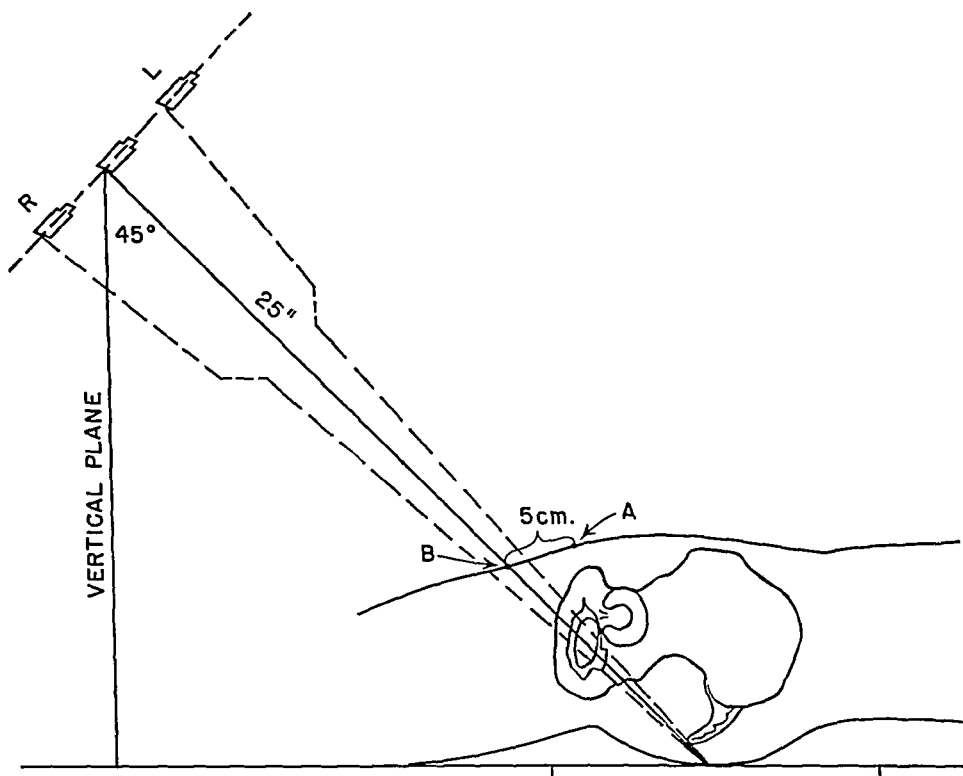


Fig. 1.—Diagram depicting direction of central x-ray beam for stereoroentgenography of the pelvic outlet.



Fig. 2.—Radiograph of pelvic outlet.

mouth-to-mouth inflation and to eliminate as far as possible the limitations and disadvantages of that method. It was originally intended for resuscitation of the newborn infant, but by the substitution of masks of larger sizes for the infant mask it has been found valuable in resuscitation of children and adults as well. It consists essentially of a hollow brass tube about seven inches in length and about  $1\frac{1}{4}$  inches in diameter which has at one end a mouthpiece and at the other a slip joint of such

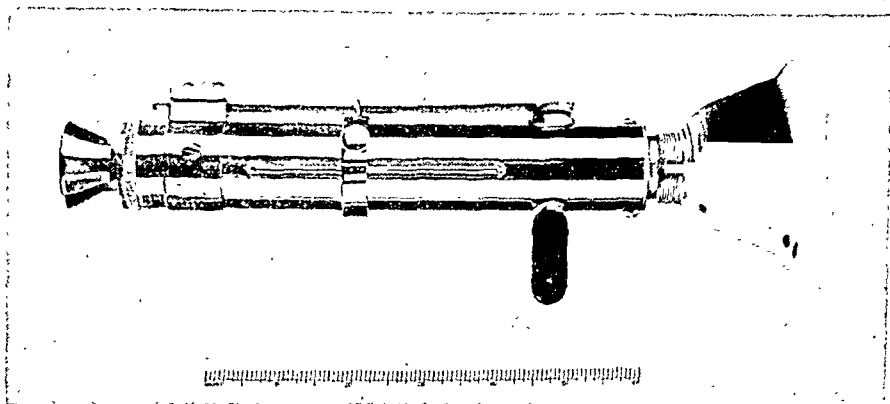


Fig. 1.—Apparatus assembled as used for full-term infants.

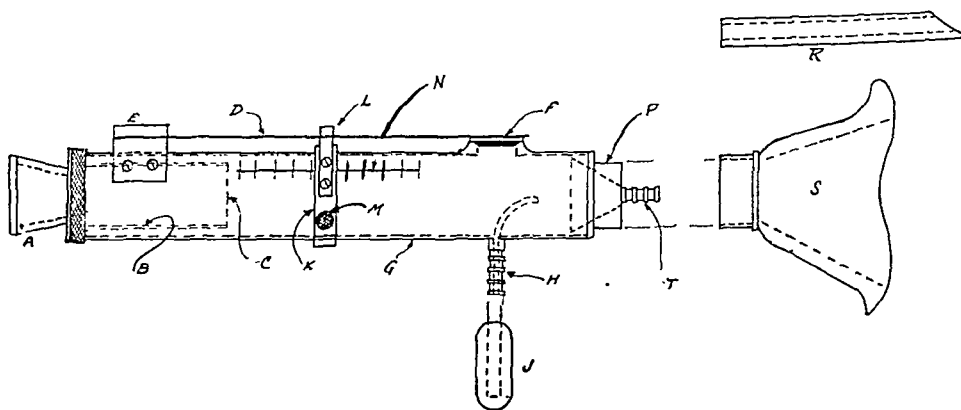


Fig. 2.—Cross section of construction. *A*, Mouthpiece. *B*, Brass capsule to be loosely filled with cotton gauze for filtration of exhalations. Sides of capsule solid but opens through gauze mesh *C*. *D*, Tension spring. *E*, Split block with set screws for securing fixed end of tension spring *D*. *F*, Tapered seated blow-off valve controlled by tension spring *D*. *G*, Brass tube  $\frac{1}{16}$  inch stock. *H*, Nipple for introduction of oxygen or for calibration of instrument using a mercury or water manometer. *J*, Rubber cover for nipple *H* when it is not in use. *K*, Sliding ring carrying rider *L* for varying tension on spring *D*. *M*, Thumb screw for fixing sliding ring and rider in position on barrel *G* according to calibration scale *N*. *P*, Slip joint for attachment of infant's face mask or adult's face mask (not shown). *T*, Nipple for attachment of soft rubber airway *R* when its use is indicated or for attachment of an endotracheal catheter (not shown).

size as to fit anesthetic masks. Distal to the slip joint is a small nipple to which may be attached a rubber airway or a small endotracheal catheter when desirable. In the mouthpiece end of the tube, a cartridge with a wire gauze screen is inserted to provide a cotton filter for the insufflated air. Cotton is better than gauze because of its superior moisture absorbing qualities. Near the mask end of the tube is a side nipple to admit oxygen or carbon dioxide-oxygen or to calibrate the instrument. This is stoppered when not in use for these purposes. On the outside of the tube is a tension spring firmly attached at the mouth-

## A SIMPLE APPARATUS FOR RESUSCITATION OF THE NEWBORN

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ASPHYXIA neonatorum has been the subject of innumerable published articles. While many of these were devoted primarily to the etiologic and physiologic aspects of the subject, a great many more have been concerned with treatment, prophylactic and active. The large number and wide diversity of methods and procedures advocated indicate that no entirely satisfactory procedure has been reported. There is, however, agreement on some general principles underlying efforts at resuscitation of asphyxiated newborn infants. First, a patent airway must be established and maintained by aspiration, postural drainage, or some other means. Second, the body temperature must be preserved and trauma avoided, especially in premature infants. Finally, until respiratory efforts begin and pulmonary ventilation is adequate, the vital functions must be supported. It is in discussion of this last subject that most of the differences of opinion have arisen.

Establishment of pulmonary ventilation by artificial respiration of some sort is the most widely practiced procedure for resuscitation of the newborn infant. It is attempted by manual methods such as squeezing the chest of the infant, by the Sylvester, Schaeffer or other maneuvers, or by smartly slapping the back. Complicated, expensive and intricate mechanical devices designed to insufflate oxygen or carbon dioxide-oxygen mixtures into the lungs or to blow the gases in and suck them out intermittently are purchasable. Mouth-to-mouth insufflation of the infant with the physician's exhaled air is the oldest, most widely used and still most generally applicable and satisfactory method of artificial respiration for infants in the newborn period.

Mouth-to-mouth inflation, widely useful as it is, still has some limitations and shortcomings. It permits no accurate control of the pressure with which the lungs are inflated. Overdistention of the chest of newborn infants by too much pressure, whether from a mechanical apparatus or mouth-to-mouth inflation, may seriously damage the lungs. During the carrying out of insufflation by this method, the operator's face is so close to the infant that it is impossible to actually observe whether the chest or stomach is being inflated and palpation may be deceiving in this respect. No provision is made for the use of oxygen-rich or variable oxygen-carbon dioxide mixtures where they may be indicated or desirable. Some individuals find mouth-to-mouth inflation esthetically distasteful. The edentulousness of the newborn usually makes it necessary to insert the finger between the gums to improve the airway and this maneuver in turn increases the difficulty in establishing an airtight contact with the face.

### DESCRIPTION OF APPARATUS

The apparatus here described (Figs. 1 and 2) is a simple and readily portable device designed to permit the application of the principles of

Its specific advantages are:

1. It facilitates the establishment of a patent respiratory airway.
2. It permits the use of a face mask designed to afford an airtight fit on the face, so as to be efficient.
3. Insufflation directly into the trachea can be provided by attaching the instrument to an endotracheal catheter at the small nipple in the mask end.
4. It is long enough to permit the operator to observe directly the amount of chest expansion occurring with each insufflation.
5. It contains a filter to afford some protection to the infant from infection through bacteria in the exhaled and insufflated air.
6. It provides accurate control of the pressure under which the insufflated air is blown into the infant's lungs.
7. Provision is afforded to insufflate oxygen or carbon dioxide-oxygen when they are considered desirable.
8. It is easily portable.
9. It can be readily sterilized.
10. It is simple to operate.
11. The pressure control spring and blow-off valve are simple in construction and unlikely to become deranged, damaged, inaccurate, or to need frequent recalibration.
12. This apparatus may be used for resuscitation of children or adults by substituting a proper size face mask for the infant's mask on the universal slip joint at the mask end.

NOTE.—Since this article was prepared the apparatus has been improved by the introduction of a guard bar over the top of the tension spring and by the substitution of a lucite mouthpiece attached to the filter cartridge and a substantial decrease in the weight of the instrument.

We are indebted to Mr. Gerard Buschenhenke who prepared the original model from submitted plans and to the Foregger Company of New York for material assistance in the calibration and testing of the instrument.

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**Burn and Withell:** A Principle in Raspberry Leaves Which Relaxes Uterine Muscle, *Lancet* 2: 1, 1941.

Raspberry leaf tea has been a herbalist's remedy for many years. Pharmacologic study of water extracts of dried raspberry leaves demonstrates that they contain a principle which relaxes the smooth muscle of the uterus and intestine when this is in tone. The action is exerted in the body of the cat and also when the muscle is suspended in a bath. The relaxation produced in the body increases with successive doses. Apparently the same principle causes contractions of the uterus of the rabbit in situ and also of the isolated uterus of the cat, rabbit, and guinea pig when they are not in tone.

CARL P. HUBER.

piece end, and ending in a tapered seat near the mask end, which covers an opening in the wall of the tube accurately and acts as a pressure exhaust control. The tension in the spring and therefore the pressure necessary to open the escape valve are controlled by a sliding ring carrying a rider over the spring. Along the side of the tube the pressure positions of the rider are calibrated.

#### METHODS OF USE

After each use the apparatus is sterilized by boiling in water. Between uses it is kept in a clean tray. When it is about to be used, sterile cotton is inserted into the cartridge and it, in turn, into the tube. The rider is adjusted toward the proximal (low pressure) end of the bar and then, holding the mask end, the mouthpiece is blown into two or three times to open the escape valve widely. When it is assured that the airway of the infant is patent, the mask is attached to the slip joint and the apparatus applied to the infant's face, so that the rubber airway intrudes into the infant's mouth between the gums and on top of the tongue. The mask is then adapted accurately to the face and held in place in the same manner as an anesthetic gas mask. The operator's small and fourth fingers, under the chin, tend to hold the infant's mandible forward while the rest of the hand holds the mask securely in place. The operator then rhythmically blows into the mouthpiece using a moderate, steady exhalation, such as one might use to blow on food to cool it. Between each insufflation the mouthpiece is removed from the mouth to permit the insufflated air to return from the infant's chest. Insufflation is at about the rate of 15 per minute. It should not be sharply expulsive exhalation or a cheek-puffing spurt of air which carries a wave of insufflation of high temporary pressure, but low volume. That the chest and not the stomach is being inflated may be determined by actual observation. When the child begins to make spontaneous respiratory efforts, it is usually unnecessary to continue the insufflation further, although if thought beneficial, oxygen may be added to the air being breathed by running it into the apparatus through the nipple near the mask end. In this case sufficient volume of oxygen should be introduced to wash out the carbon dioxide which might accumulate.

When it is thought advisable to use oxygen or carbon dioxide to insufflate before breathing has begun, it is carried out by admitting the gas through the side nipple and holding the palm of the hand over the mouthpiece end, placing it on and off rhythmically and intermittently in the same manner as the mouth-to-tube inflation described above. In this manner, the infant's lungs are intermittently inflated with the gas chosen. If it is deemed advisable to use an endotracheal catheter and insufflate the air or gas directly into the trachea, the mask and rubber airway are removed and the apparatus attached directly to the catheter at the small nipple on the mask end. For resuscitation of seriously asphyxiated infants, particularly of the pallid type, we prefer endotracheal insufflation. It must be remembered that if insufflation is made directly into the trachea less pressure will be needed to expand the lungs adequately than with the mask alone, or mask and airway.

#### SUMMARY

An apparatus is described to apply the principles of mouth-to-mouth insufflation for resuscitation of the newborn.



quently the effect of rupture of the membranes in early labor, or even at term after the physical conditions described above are attained, cannot be evaluated at present. To use it as an argument against a theory which has never been promulgated is, therefore, unjustifiable.

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### Reply by Dr. Bickers

*To the Editor:*

I wish to take this opportunity to reply to Dr. S. R. M. Reynolds.

Dr. Reynolds apparently is concerned because he feels that I have attempted to disqualify certain statements which he has made regarding the cause of the onset of labor. It was not my intention to suggest that Dr. Reynolds believes that the distention factor is the only mechanism operating in the onset of labor contractions. Since my study was confined purely to the mechanical factors and made no attempt to investigate the endocrine, humoral, and cytologic changes, I was interested only in the physiologic alterations due to change in the intra-uterine pressure.

I have studied Dr. Reynolds' letter with a great deal of care and frankly must admit that I cannot quite make him out. It will be noted from my paper that my language was very conservative. I said, "It has been *suggested* that the onset of labor may result from distention." Later I said, "Artificial rupture of membranes at term will induce labor which *tends* to invalidate the distention theory." I think that no one will deny the accuracy of these statements. I did not mention all of the other factors related to the onset of labor because they were not in the scope of this study.

Dr. Reynolds' more recent publication, which describes the increased uterine tension near term, is a real contribution to the subject and my investigations, not yet published, are thoroughly in accord with his. I cannot agree with Dr. Reynolds when he says that artificial rupture of membranes and its effects, which are so well known, cannot be used as an argument against the distention theory.

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RICHMOND, VA.

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The sudden and untimely death of Dr. Hugo Ehrenfest occurred on July 24. An obituary will appear in the next issue of the JOURNAL.

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## Correspondence

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### Kymograph Records of Uterine Contractions

To the Editor:

In the May issue of this JOURNAL (47: 815, 1942) appears an article by William Bickers, entitled "A Study of Contractions in Labor Based on Kymographic Records Obtained From an Intrauterine Balloon." It is based on data from four patients. This article contains a statement of interest to me, since it misinterprets and attempts to disqualify certain views and facts which I have advanced. This would be of no significance were it not that several other investigators and clinicians have likewise misconstrued my views in this respect from time to time.

The above article states: "It has been suggested that the onset of labor may result from distention, which puts the muscle fibers under tension; ischemia results and contractions follow." This is represented as the view of the undersigned, as expressed in Chapter XII in my monograph, *Physiology of the Uterus* (Hoeber, 1939). It is dismissed by the following statement: "The well-known fact that artificial rupture of the membranes at term will induce labor tends to invalidate the distention theory as a cause of labor."

The facts of the situation are as follows: In the above-mentioned chapter, an evaluation is made of the physiologic relationships in the uterus at term. In the initial sentence, the following statement appears: "There is no known single cause for the onset of labor as the numerous theories of the past and present imply. Rather, it now seems that parturition begins as a result of the gradual, accelerating convergence of a number of factors, structural, humoral, nervous, nutritional, and circulatory, which, at a time characteristic for each species and adapted to the morphologic conditions present in each, are so associated that they lead to evacuation by the uterus of its contents." A clearly speculative, tentative and hypothetical set of physiologic relationships is then given diagrammatically. The scheme refers to distention factors (which clearly exist), hormonal factors (which have never been denied), metabolic conditions in the myometrium (that are seldom considered), the rudiments of simple muscle physiology (which are affected by either a balloon in the uterus at term, or by rapid loss of fluid from rupture of the membranes), and other factors. The following statement also appears: "Physiological coordinating factors—unknown." In the face of these factual considerations, a "distention theory" for the onset of labor, based on these views written in 1938 and published early in 1939, is ascribed to me today. *There is no "distention theory."*

To quote my views more correctly, Dr. Bickers should have referred to a paper entitled: "Physical Conditions in the Uterus Governing the Duration of Pregnancy," published late in 1939 (*Anatomical Record* 75: 175-190). The essence of this work, established by measurements, is that until shortly before the onset of labor, the tensions on the uterine wall are different in different parts; this is apparently provided for by several mechanisms, structural, physical, and hormonal. As term approaches, the "slack" is progressively taken up, and the maximal uterine tension becomes about uniform over the surface of the whole organ. The significance of this condition is given in the following quotation: "This appears to be, accordingly, the physical condition at the end of gestation which signals impending parturition." But what happens later, amid a complexity of conditions, to effect coordination of uterine contractions in labor remains as unknown as ever. Conse-

80 per cent of infants are nursed may expect a first-year mortality of 4 per cent at least. Poor nursing has a greater infant mortality than poor delivery. The author emphasizes that pumping the breasts after nursing keeps up full production of milk. The milk intake of 1,720 spontaneously newborn infants was studied through their second to ninth days, as well as the residual milk pumped from the breasts after nursing. Maternal production in general showed a much greater fluctuation than infant intake. More women had excess milk than deficient production. Of primiparas, those under 20 had quantitatively the best production. In multiparas milk secretion increased with parity. The onset of lactation occurs sooner in younger women and in multiparas. After spontaneous delivery, 90 per cent of this series of women were capable of nursing their infants.

R. J. WEISSMAN.

Folley, S. J., and Young, F. G.: Prolactin as a Specific Lactogenic Hormone, *Lancet* 1: 380, 1941.

The authors review the available information concerning the role of the anterior pituitary gland in the production of lactation and emphasize that there are differences between the pigeon crop gland-stimulating (prolactin) and galactopoietic activities of anterior pituitary extracts. These differences are important in considering the clinical use of anterior pituitary preparations in women in whom lactation is deficient and perhaps explain differences in clinical results reported by various authors as the preparations used have been assayed for prolactin effect only. The authors suggest testing such materials for their galactopoietic effect on mammals.

CARL P. HUBER.

Fauvet, E.: Study of Lactation, *Zentralbl. f. Gynäk.* 65: 580, 1941.

The author feels that the goal of those attempting endocrine control of lactation is unattainable. Many workers lose sight of the stimulating effect of suckling. Fauvet covered half the teats of a group of nursing dogs with tape and compared the resulting typical microscopic picture of a regressive mammary gland with that of the normally active glands thirteen and fourteen days after delivery. When the pups were allowed to suckle the previously covered breasts, they returned to full functional activity. From this standpoint, says Fauvet, the problem is not as dependent on the action of lactogenic hormone as endocrinologists would have us believe. As with cows, full function of the glands depends on a nourishing diet and complete emptying of the breasts.

R. J. WEISSMAN.

Lehmann, G.: A New Means of Increasing Lactation During the Puerperium, *Zentralbl. f. Gynäk.* 64: 1480, 1940.

Lehmann reviews briefly the endocrinology and physiology of lactation. The lactation inhibiting effect of follicle hormone is well understood. In cases in which renal excretion of the hormone is delayed post partum, lactation is usually inhibited. In 1,056 uncomplicated births, lactation was adequate in 82 per cent. In 20 eclamptics, lactation was adequate in 25 per cent. These findings gave the author the notion of administering a purine diuretic in cases of poor or average lactation, in order to increase the rate of renal elimination of the follicle hormone. As an added proof of the author's premise, it was found that abundance of lactation was in direct relation to the amount of blood lost at delivery. In the group of mothers losing over 1,500 Gm. of blood all had abundant lactation.

# Department of Reviews and Abstracts

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CONDUCTED BY HUGO EHRENFEST, M.D.

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## Selected Abstracts

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### Mammary Glands

Engel, Stefan: Anatomy of the Lactating Breast, Brit. J. Child. Dis. 38: 14, 1941.

Impossibility or reduced ability of breast feeding is influenced by many factors. There are not only the physical state of the mother, nutrition, occupation, fatigue, etc., but also hormonal and psychical conditions to be taken into consideration. Also the stimulus of suckling is an important factor. The basic condition, however, is the milk-producing gland itself, which, in view of obvious difficulties so far, has not been sufficiently studied from the anatomic viewpoint.

In this paper the author reports careful investigations made on the breasts of 26 women who had died during labor or within the next few days. These investigations showed considerable differences in the structure of lactating breasts, varying from the normal breasts to those provided only with a small or even negligible amount of glandular tissue. Functional inability therefore often is fully explained morphologically, a point of great importance for therapeutic efforts to increase the milk output.

HUGO EHRENFEST.

Fredrikson, H.: Endocrine Factors Involved in the Development and Function of the Mammary Glands, Acta obst. et gynec. Scandinav. 20: 293, 1940.

From experimental studies on rabbits, Fredrikson concludes that in the absence of the pituitary gland, the development of the breasts is directly dependent on the action of the ovarian hormones. In addition, he has shown that the purified preparation of prolactin, which exhibits no gonadotropic, thyrotropic or adrenal activity can induce lactation in spite of the absence of the pituitary gland. Therefore, this prolactin can be substituted for the anterior lobe of the pituitary with regard to the excitation of lactation.

J. P. GREENHILL.

Feldweg, P.: Contribution to the Physiology of Nursing, Zentralbl. f. Gynäk. 65: 585, 1941.

Feldweg believes that all newborn infants should receive mother's milk, and if the supply is not sufficient, it should be supplemented by wet nurse milk. The mortality of infants on artificial food is five to ten times as great as of those receiving breast milk. According to the author's figures, about 3 per cent of all nursing infants die during their first year as opposed to a 15 to 30 per cent mortality of nonnursing or poorly nursed infants. The average clinic in which 50 to

examination revealed voluminous breasts. A few red blood cells were present in the milk first obtained from the left breast. The uterus was slightly smaller than normal, firm, and in normal position.

Chiari and Frommel's disease exhibits persistent lactation associated with utero-ovarian atrophy, the degree of atrophy varying in different cases. Menstruation may not recur after weaning, depending on the degree of atrophy.

The case presented is not regarded as true Chiari or Frommel's disease since the uteroovarian atrophy was of minor nature. The daily manipulation of the breasts may have been quite influential in prolonging lactation.

FRED L. ADAIR AND WILLIAM ROSENBAUM.

**Anderson, A. B., and Brown, Alexander:** Tetany Following Prolonged Lactation on a Deficient Diet, *Lancet* 2: 482, 1941.

The authors report a patient, 42 years of age, para ii, who developed definite tetany during a lactation period of twenty-one months. Her diet had been inadequate. Treatment with a high-calcium milk diet resulted in rapid recovery and was in striking contrast to the lack of response to therapy in those cases where tetany is due to failure of calcium absorption. The authors suggest that calcium deficiency is common in lactating women.

CARL P. HUBER.

**Spoor, Hartman, and Brownell:** Cortilactin, the Lactation Factor of the Adrenal, *Am. J. Physiol.* 134: 12, 1941.

A lactation factor was prepared from the adrenals by isoelectric precipitation. The pigeon crop gland response was used for its assay. The best cortilactin preparation possessed about one-tenth of the potency of purified prolactin when tested by the crop gland method. The daily injection of 1 mg. of the cortilactin preparation into an adrenalectomized female rat, maintained on cortin, enabled her to lactate normally.

J. P. GREENHILL.

**Preisseecker, E.:** Influence of Male Sex Hormone on the Female Breast, *Zentralbl. f. Gynäk.* 64: 999, 1940.

The author gave "physiologic" doses of testosterone to nursing mothers at periods varying from ten days to three months post partum. An increase in milk secretion was noted in all cases, in his opinion as a result of the antagonism of testosterone to the lactation inhibiting follicular hormone.

R. J. WEISSMAN.

**Nathanson, Meigs, and Parsons:** The Treatment of Mammary Pain and Secretion With Testosterone Propionate, *New England J. Med.* 226: 323, 1942.

Testosterone propionate was administered to 30 carefully selected patients with severe mammary pain and secretion. It was found to be an effective agent in the relief of the syndromes in a high percentage of the cases. It appears to be more efficient than the estrogenic hormone in the treatment of the same lesions. Recurrence of symptoms is the rule, usually within six months after medication is discontinued. Prolonged and continuous treatment especially with large doses is to be discouraged. Periods of treatment should be followed by adequate rest

Novophyllin was given to 64 mothers in 3 doses in the first twelve hours post partum. Each received 1,500 c.c. total fluids daily. There was a notable average increase in both amount and specific gravity of the urine. Then the drug was given to a group of 396 mothers; 93.2 per cent had abundant lactation and 6.8 per cent moderate lactation. An untreated group of 539 mothers had abundant lactation in 72.0 per cent, moderate in 27.6 per cent, and no lactation in 0.2 per cent. Larger doses of the diuretic increased the percentage of those said to have abundant lactation. Comparison of the daily average milk secretion showed the diuretic treated mothers to be secreting 13 to 123 Gm. more milk per day. The effect of the medication was definitely evident up through the ninth post-partum day. The weight of children on the ninth day was 30 per cent in excess of birth weight as compared with an increase of 15 per cent for the children of untreated mothers. Lehmann felt that his results were good enough so that there was no need of risking a trial with mercurial diuretics. If the medication works too well the secretion can be controlled by small doses of follicle hormone.

R. J. WEISSMAN.

**Menju, K.:** The Effect of Visible Light Upon the Secretion of Milk, *Jap. J. Obst. & Gynec.* 23: 130, 1940.

In cases in which the breasts were irradiated with infrared rays, the secretion of milk was increased. On the other hand, irradiation of the breasts with blue rays retarded the flow of milk. Irradiation with white light had no effect. When the heads of experimental animals were subjected to irradiation with infrared rays, the flow of milk was increased, but no effect was observed when the blue or white rays were used. The author concludes that the effect of light on the secretion of milk is produced by way of the vegetative nervous system and the endocrine glands.

J. P. GREENHILL.

**Olsen, A.:** Nursing Under Conditions of Thirst or Excessive Ingestion of Fluids, *Acta obst. et gynec. Scandinav.* 20: 313, 1940.

Thirteen nursing mothers were given daily amounts of fluid varying from 600 to 2,775 c.c. and daily determinations were made of the total amount of breast milk obtained. Only one of the 13 women showed a parallelism between the increase in the amount of fluid taken and the increased production of milk. In all the others there was no such relation between the fluid intake and the milk output observed. Five women were very thirsty when their fluids were restricted, but this had no effect on the amount of milk excreted. In fact, one of these women had a remarkable increase in milk. The infants showed no effect from restriction of fluids in the mother. The author concludes that the supply of breast milk cannot be increased by having a woman take more fluid nor can the amount of milk be cut down by curtailing the ingestion of fluids.

J. P. GREENHILL.

**Gilber, Barton:** Persistent Lactation With a Note on Chiari and Frommel's Disease, *Brit. M. J.* 2: 305, 1941.

The history of a 35-year-old married woman showing lactation continuing over fifteen years following childbirth is reported. She had persistently manipulated or expressed her breasts during this time believing it normal to lactate the entire reproductive period following childbirth. Her menses had recurred six months after childbirth at monthly intervals, lasting four days with each period. Physical

not the ovaries are present. At least one androgen, testosterone, also inhibits lactation and has the power of stimulating mammary growth.

Estrogens are also capable, under suitable conditions, of enhancing milk secretion by increasing the concentration of both fatty and nonfatty solids. The threshold for the enrichment effect is lower than for inhibition. These two effects are more readily separable with natural estrogens than with diethylstilbestrol.

CARL P. HUBER.

**Noble, R. L., and Collip, J. B.:** Regression of Oestrogen Induced Mammary Tumors in Female Rats Following Removal of the Stimulus, *Canad. M. A. J.* 44: 1, 1941.

Mammary tumors produced in rats by the subcutaneous implantation of estrone pellets showed marked cellular hyperplasia but were all localized and showed little tendency to invade the stroma or adjacent tissue. Continuous growth occurs until the animal's death, provided the pellets remain intact. Attempts to transplant the tumors into other rats have failed but in two cases homotransplants grew successfully. Lung metastases were found in one rat with advanced tumor formation of nine months' duration. Cellular infiltration of a typically malignant appearance was encountered in a few cases. Four rats treated with progesterone showed cessation of tumor growth. In 4 rats from whom the estrone pellets were removed, the tumors completely regressed. One of these animals had an ulcerated primary mammary tumor with a histologic picture of malignancy and a successful homotransplant. After long periods nearly all animals were found to have large pituitary adenomas, and in 2 rats large hemorrhagic adenomas developed during the first year of treatment.

CARL P. HUBER.

**Wirth, Karl, and Peters, Max:** Report on the Roentgen Ray Treatment of Early Puerperal Mastitis, *München. med. Wchnschr.* 86: 59, 1939.

Wirth and Peters present their results and experiences in treating patients with an early infiltrative mastitis by using soft roentgen rays, giving 10 to 20 per cent skin erythema doses. Treatment, they believe, must begin within forty-eight hours of the onset of symptoms. In patients in whom infiltrations have occurred and nodules have formed, and in cases of interstitial mastitis the roentgen ray treatment promises but little success; in fact, it may even lead to more necrosis of the tissues thus causing retardation of recovery because of the chronic, inflammatory edema resulting.

The value of using roentgen therapy in the early cases must not be overestimated, however, since these inflammations also recede quickly under ordinary treatment. The advantages of the roentgen therapy lie in the fact that pain disappears quickly and the patient is able to continue nursing her baby.

C. E. PROSHEK.

**Antoine, T.:** Endocrine Influences on Lactation, *Zentralbl. f. Gynäk.* 65: 465, 1941.

The author emphasizes that the problem of regulating lactation therapeutically is a complex one depending upon the multiple influences initiating lactation in the first place. With some of the endocrines now available the problem is mainly one of dosage, while with others the mechanism of inhibition or increase of lactation is obscure. The vitamin status of the gravid and post-partum woman is of more than minor significance.

periods. Many patients present a dominant psychogenic element, and others have spontaneous remissions, therefore, patients should be carefully selected for this treatment.

HUGO EHRENFEST.

Duffy, Paul V., and Corsaro, Joseph: Suppression of Lactation by Testosterone, J. A. M. A. 116: 33, 1941.

The authors report encouraging results by the use of testosterone in the suppression of lactation post partum. In 18 cases in which the breasts were definitely engorged, tender, and painful, the administration of testosterone was begun on the third or fourth day post partum. Dosage ranged from 15 to 75 mg., the largest quantity given at any single injection being 25 mg. Tenderness was relieved promptly, and lactation was suppressed in twenty-four to forty-eight hours. Similar quantities of testosterone were ineffective in suppressing lactation in 4 cases in which it had already been definitely established when treatment was begun. The treatment also failed in 3 cases in which 25 mg. were administered immediately after delivery. It has been found that methyl testosterone given orally will produce comparable results (25 mg. three times daily for 6 doses).

It appears that the pituitary depression caused by moderate doses of testosterone administered at the initiation of the secretory phase of the breasts is sufficient to inhibit lactogenic function of the pituitary gland and to suppress lactation.

WILLIAM BERMAN.

Fleischer and Kushner: Inhibition of Lactation. Percutaneous Use of Testosterone, J. Clin. Endocrinol. 1: 407, 1941.

Studies of the authors showed that male sex hormone administered by inunction was effective in 68 per cent of cases in whom for one reason or another inhibition of lactation was desirable. It was only partially effective in 29 per cent of the cases. It was entirely without effect in 3 per cent. In no case was lactation entirely arrested. The effect was rather a diminution in the degree of lactation with resulting diminution of secondary signs and symptoms, such as engorgement and pain. Testosterone, percutaneously, can successfully be used for the inhibition of lactation.

J. P. GREENHILL.

Spence, A. W.: Local Inunction of Testosterone in Chronic Mastitis, Lancet 2: 387, 1940.

Testosterone or testosterone propionate administered by inunction in daily doses of 3 to 10 mg. gave relief of pain to 8 patients with chronic mastitis. In 2 patients relief was obtained with inert ointment as well, but in the remaining 6 this was ineffective. The author points to the small dosages and absence of side-effects as advantages of this method in comparison with similar therapy by injection.

CARL P. HUBER.

Folley, S. J.: Effects of Estrogens on Lactation, Lancet 1: 40, 1941.

It is now an accepted fact that the administration of estrogen stimulates growth of the mammary ducts and in some species the lobule-alveolar system, though it is not clear whether the effect is direct or is mediated through the anterior pituitary. It is further known that estrogens will inhibit lactation. This occurs whether or



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The author gave *stilbene* (Cyren) to 80 post-partum women who did not wish to nurse their infants, beginning the first puerperal day. Of them 47 received the drug in ointment form percutaneously, while the remainder required either 10 mg. doses intramuscularly or 12 mg. by mouth, to inhibit lactation. In another group of women, breast fullness and pain was relieved by doses of 0.75 mg. intramuscularly. Percutaneous application of the ointment to only one breast was effective. The unmedicated breast gave no evidence of swelling or lactation.

In the author's clinic 207 women received *progynon* in doses from 50,000 to 600,000 units, averaging 100,000 to 500,000, in the last weeks of pregnancy; 86 per cent were able to nurse their infants, the rest had their offspring on complementary feeding or on full formula. High doses are not to be feared.

Conflicting reports of the effect of *testosterone* on lactation should not discourage further work along this line, for the answer here lies in sufficient dosage. Antoine suggests an analogy of the inhibitory effect of pituitary irradiation on menorrhagia and the stimulating effect of light doses in amenorrhea.

Diuretic therapy has been found effective in cases of insufficient lactation. Thyroid as well as *purines* have been given with excellent results. *Prolactin* has failed with many, principally because of low dosage. When prolactin fails in spite of high doses, one must look to estrone and progesterone deficiencies which have failed to develop a competent glandular structure. Prolactin, incidentally, has been found in most of the organs and tissues of man; in the placenta from the third to eighth months, in the decidua, in the fluid of hydatid moles, also in newborn infants.

R. J. WEISSMAN.

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## Item

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### American Board of Obstetrics and Gynecology

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Saturday, February 13, 1943, at 2 P.M. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination held later in the year. All applications must be in the office of the Secretary by November 16, 1942.

Effective this year there will be only one general classification of candidates, all now being required to have been out of medical school not less than eight years, having in that time completed an approved one year general rotating internship and at least three years of approved special formal training, or its equivalent, in the seven years following the interne year. This Board's requirements for internships and special training are similar to those of the American Medical Association since the Board and the A. M. A. are at present cooperating in a survey of acceptable institutions. All candidates must be full citizens of the United States or Canada before being eligible for admission to examinations.

All candidates will be required to take the Part I examination, which consists of a written examination and the submission of twenty-five (25) case history abstracts, and the Part II examination (oral-clinical and pathology examination). The Part I examination will be arranged so that the candidate may take it at or near his place of residence, while the Part II examination will be held late in May, 1943, in that city nearest to the largest group of applicants. Time and place of this latter will be announced later.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

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\*Deceased, June 18, 1942.

### Erratum

In the review of the book on "Hernia" in the May, 1942, issue of the JOURNAL, page 904, the author's name should be "Iason" instead of "Jason."

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TABLE OF CONTENTS ON PAGE 6

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## CONTENTS FOR SEPTEMBER, 1942

|  |     |
|--|-----|
| In Memoriam—Hugo Ehrenfest, 1870-1942..... | 367 |
|--|-----|

## Original Communications

|   |     |
|---|-----|
| The Pulse and Respiratory Rates During Labor as a Guide to the Onset of Cardiac Failure in Women With Rheumatic Heart Disease. Curtis L. Mendelson, M.D., and Harold E. B. Pardee, M.D., New York, N. Y. ....   | 370 |
| True Bone Formation in the Fallopian Tube. E. W. Kulka, M.D., New York, N. Y. ....  | 384 |
| Transplantation of Fascia for Relief of Urinary Stress Incontinence. Albert H. Aldridge, B.S., M.D., F.A.C.S., New York, N. Y. ....   | 398 |
| Adenomyosis of the Fallopian Tube. Donald H. Wrook, M.D., and Albert C. Broders, M.D., Rochester, Minn. ....  | 412 |
| Does the Antenatal Use of Vitamin K Prevent Hemorrhage in the Newborn Infant? John Parks, M.D., and Lewis K. Sweet, M.D., Washington, D. C. ....  | 432 |
| Pregnadiol Determinations in Gynecology and Obstetrics. E. C. Hamblen, M.D., W. Kenneth Cuyler, Ph.D., and Margaret Baptist, Durham, N. C. ....   | 442 |
| Clinical Experiments in Relation to the Excretion of the Estrogens. I. Urinary Estrogens Before and After the Injection of Estrone Into a Patient With Surgical Menopause. George Van S. Smith, M.D., O. Watkins Smith, Ph.D., and Sara Schiller, B.S., Brookline, Mass. .... | 455 |
| The Histopathologic Diagnoses of the Atypical Endometrium. Bernard Mann, M.D., David R. Meranze, M.D., and Leib J. Golub, M.D., Philadelphia, Pa. ....  | 460 |
| Use of Sulfanilamide Powder in Gynecologic and Obstetric Operations. John D. Bibb, A.B., M.D., New York, N. Y. ....   | 464 |
| Origin of Endometriosis From the Mesenchyme of the Celomic Walls. Peter Gruenewald, M.D., Chicago, Ill. ....  | 470 |
| The Use and Potency of Synthetic Estrogens. J. P. Greenhill, M.D., Chicago, Ill. ....   | 475 |
| Urinary Infection in Pregnancy Due to Flexner Dysenteriae. A. W. Diddle, M.D., and A. P. McKee, M.D., Iowa City, Iowa ....  | 481 |
| Primary Peritoneal Pregnancy. William E. Studdiford, M.D., New York, N. Y. ....   | 487 |
| Pseudomyxoma Peritonei. Henry W. Erving, B.A., M.D., Pittsburgh, Pa. ....   | 492 |
| Chorionepithelioma. Malcolm B. Dockerty, M.D., and Winchell McK. Craig, M.D., Rochester, Minn. ....   | 497 |
| Hydatid Mole With a High Persistent Titer of Gonadotropic Hormone. Owen Jones Toland, M.D., Philadelphia, Pa. ....  | 502 |
| The Elderly Primigravida. Philip B. Wahrsinger, M.D., and J. Irving Kushner, M.A., M.D., New York, N. Y. ....   | 505 |
| Incidence of Placenta Previa During a Ten-Year Period at Cleveland Maternity Hospital (1931-1940). J. L. Reycraft, M.D., and Charles P. Platz, M.D., Cleveland, Ohio ....   | 509 |
| Adenocarcinoma With Ovarian Metastases. Clayton T. Beecham, B.S., M.D., and Rupert H. Friday, B.A., M.D., Philadelphia, Pa. ....  | 512 |
| Pregnancy Following Operation for Congenital Absence of Vagina. W. Stewart Whittemore, M.D., F.A.C.S., Cambridge, Mass. ....  | 516 |
| Fibroma of the Ovary. Simon Brody, M.D., Brooklyn, N. Y. ....   | 521 |
| Bilateral Ovarian Dermoid Cysts Complicating Pregnancy Treated by Bilateral Oophorectomy. Robert H. Goodwin, A.B., M.D., F.A.C.S., New Bedford, Mass. ....  | 525 |
| Primary Ovarian Pregnancy. William B. Evans, M.D., George B. Sichel, M.D., and Joseph L. Ivins, M.D., Chester, Pa. ....   | 528 |

## Department of Practical Problems in Obstetrics and Gynecology

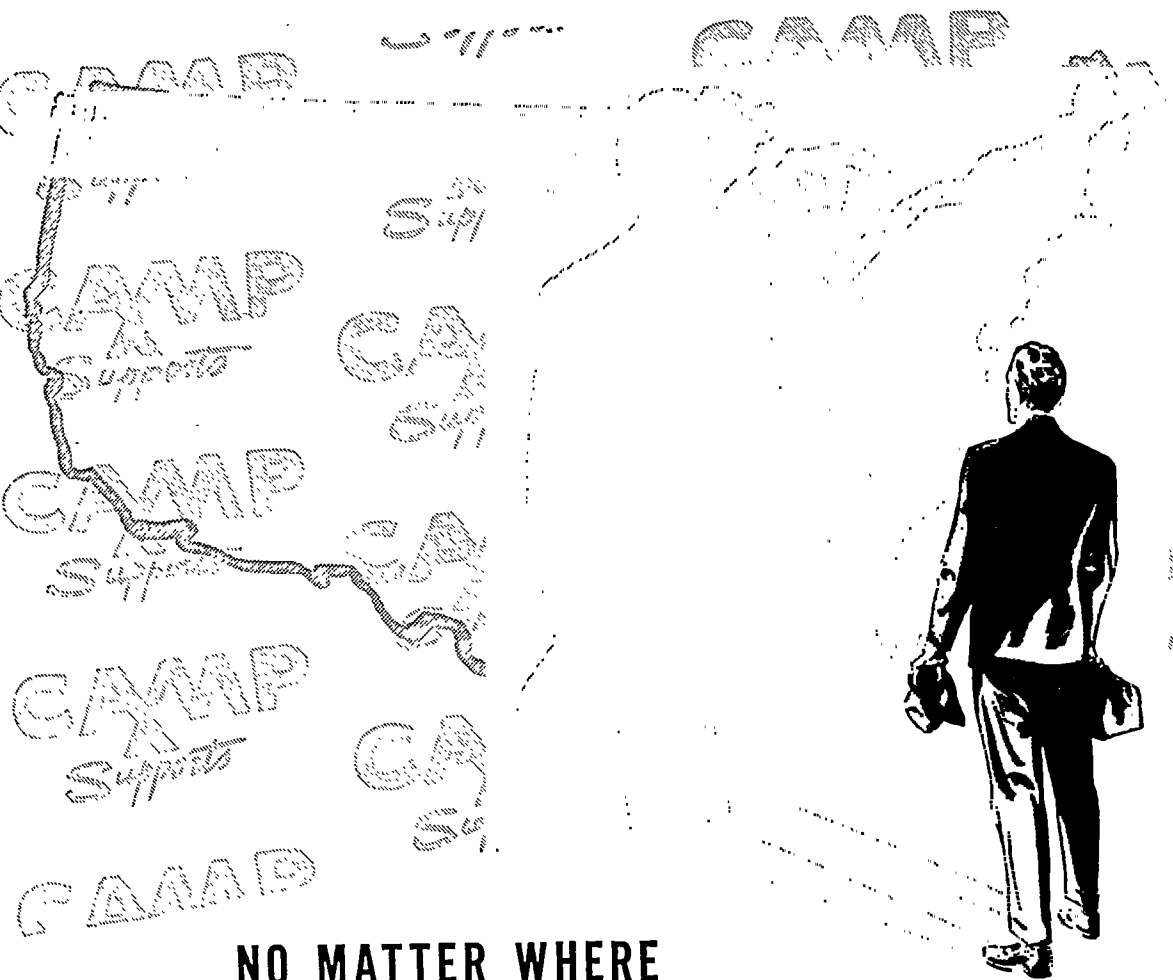
|   |     |
|---|-----|
| Treatment of Bleeding in the First and Third Trimesters of Pregnancy. H. J. Stander, M.D., New York, N. Y. .... | 531 |
|---|-----|

## Society Transactions

|   |     |
|---|-----|
| New York Obstetrical Society, Meeting of March 10, 1942 .....                     | 542 |
| Obstetrical Society of Philadelphia, Meeting of December 4, 1941 .....            | 542 |
| Meeting of March 5, 1942 .....  | 542 |
| Obstetrical Society of Boston, Meeting of January 20, 1942 .....                  | 542 |
| Meeting of February 17, 1942 .....  | 543 |
| Pittsburgh Obstetrical and Gynecological Society, Meeting of April 13, 1942 ..... | 543 |

## Department of Reviews and Abstracts

|  |     |
|--|-----|
| Selected Abstracts—Menstruation .....                  | 544 |
| Announcement—A Registry of Ovarian Tumors .....        | 551 |
| Item—American Board of Obstetrics and Gynecology ..... | 552 |



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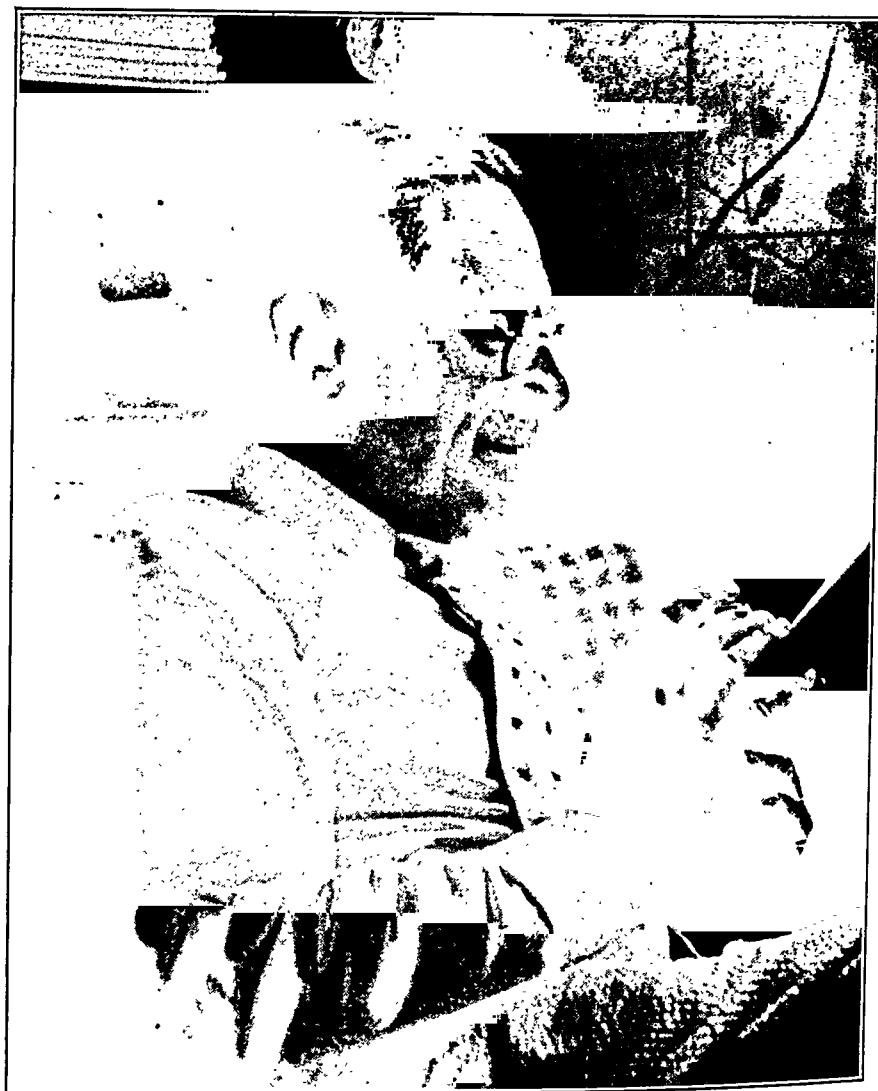
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Hugo Ehrenfest  
1870—1942



From 1908 until he retired as consultant in 1936, he directed the organization and policies of the division of obstetrics and gynecology at the Jewish Hospital and was largely instrumental in setting up the standards at that institution.

His contributions to the literature of our specialty were numerous. He wrote chapters in Peterson's "Textbook of Obstetrics," in Davis' "Obstetrics and Gynecology" in Nelson's "Loose-Leaf Practice of Medicine," and in Crossen's "Diseases of Women," besides writing many journal articles. In 1925 he translated and prepared an American edition of Koehler's "Therapy of Puerperal Fever."

As a scientist Ehrenfest concentrated his interest in the field of obstetrics. He contributed much to the technique of pelvimetry and to the knowledge of the diseases complicating pregnancy, but his most outstanding work was his volume on "Birth Injuries of the Child," contributed to the Appleton Monograph series (1922). He was literally an encyclopedia of knowledge on almost every subject in obstetrics. It was this painstaking and comprehensive investigation combined with an ability to analyze and correlate his data that has made the monograph on birth injuries the outstanding work on this subject.

His teaching experience dated back to 1904. During the 16 years he served as professor at St. Louis University and the 20 years he was teaching at Washington University, he instructed many students of medicine. His influence in the development of sane, conservative obstetrics in this large group was most beneficial. He scrupulously avoided fads and opposed the indiscriminate use of twilight sleep, cesarean section, Dührssen incisions, etc. "Meddlesome midwifery" was in his opinion the cause of the persistently high maternal and infant mortality, and in the well-known Conference on Child Welfare held in President Hoover's administration, he was chairman of the special committee dealing with this subject. He was an unusually effective teacher not merely because of the clear analytical method of expressing his ideas but because of the droll and amusing way in which he embellished them from the wealth of his personal experience.

Even more important than his contributions as scientist and teacher was his work as editor. With amazing rapidity after coming to this country, he acquired a mastery of the English language and correct diction. It was not long before he was correcting our use of English instead of our correcting his. As one of the editors of the *Interstate Medical Journal*, and since 1920 as associate editor and later as co-editor of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, he spent a lifetime in correcting and clarifying innumerable scientific articles contributed to these journals. The number of grammatical errors in our papers that he has picked up and deleted are legion. We should all of us be grateful to him for having helped us in this thankless job of making our contributions more intelligible and less wordy.

# American Journal of Obstetrics and Gynecology

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## In Memoriam

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HUGO EHRENFEST

1870-1942

**H**UGO EHRENFEST died July 24, 1942. Although he had in the past few years had occasional symptoms of angina, this had not incapacitated him from his duties as obstetrician and co-editor of the JOURNAL. After the usual busy morning at the hospital and in the office he went home to take his afternoon siesta and without arousing passed peacefully from slumber to death.

Born in Vienna 72 years ago, he took his doctor's degree at the University in that city in 1894. He served as assistant in Professor Schauta's obstetrical clinic at the Allgemeine Krankenhaus from 1896 to 1899. In 1900 he came to America and settled in St. Louis, where his friend, the late George Gellhorn, well-known gynecologist, had preceded him by one year. He rapidly adapted himself to his new home, and in 1904 married Sophie Schwab, a member of an old St. Louis family, who with two sons and a daughter survive him. He rapidly became a leader in his specialty. In 1904 he was appointed assistant professor of obstetrics and gynecology at St. Louis University and in 1907 was elected a Fellow of the American Gynecological Society, serving as vice-president of this Society in 1921. He was also a member of the Central Association of Obstetricians and Gynecologists and the St. Louis Gynecological Society. From 1904 to 1920 he taught at St. Louis University School of Medicine, being head of his department for a large part of that period. In 1922 he became associate professor of obstetrics and gynecology at Washington University School of Medicine, where he was engaged in teaching until the time of his death. From 1936 on he held the title of Professor Emeritus. His hospital appointments were at the Jewish Hospital, St. Louis Maternity Hospital, and Barnes Hospital.

## Original Communications

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### THE PULSE AND RESPIRATORY RATES DURING LABOR AS A GUIDE TO THE ONSET OF CARDIAC FAILURE IN WOMEN WITH RHEUMATIC HEART DISEASE

CURTIS L. MENDELSON, M.D., AND HAROLD E. B. PARDEE, M.D.,  
NEW YORK, N. Y.

*(From the Departments of Obstetrics and Gynecology and of Medicine of the New York Hospital and Cornell University Medical College)*

IN A previously reported study<sup>1</sup> of the pulse and respiratory variations of 180 normal women during labor, it was observed that the pulse and respirations remained practically unchanged throughout the first stage of labor. With the advent of bearing down efforts in the second stage of labor 4 per cent of patients showed a rise of the pulse rate to above 110 per minute with respirations of not over 24 per minute. Such elevations were considered as established only when they persisted for at least forty-five minutes. Thirteen per cent showed a rise in the respiratory rate to above 24 per minute with the pulse rate not over 110, and 7 per cent showed a rise of both pulse and respiratory rates above these values. The levels of 110 and 24 were chosen arbitrarily since a large percentage of patients approached or reached these values but relatively few exceeded them. Prolonged labor and prolonged second stage were found to predispose to such rises but no definite influence of analgesia or of the particular analgesic used could be observed.

We have extended these studies to women with rheumatic heart disease to note if their pulse and respiratory variations during labor differed in any way from those of normal women so as to give a warning of the approach of serious cardiac insufficiency. The 200 patients studied were first seen in the ante-partum clinic at various stages of their pregnancy. The diagnosis of the particular form of heart disease was made at this time and sometimes was amended as later observations seemed to indicate. The patients were classified as to their functional capacity (Class 1, 2, 3, or 4) according to the criteria of the New York Heart Association, and as they were followed progressively in the ante-partum clinic, this diagnosis was changed as indications seemed to warrant.

At the onset of labor or as soon thereafter as the patient was admitted to the hospital, the pulse and respirations were counted every fifteen minutes between pains and charts made of this similar to those appear-

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

To those who knew Hugo Ehrenfest intimately, he was a man of many accomplishments and a genial personality. The charm of Vienna, where so many of us spent happy and profitable days in the past, was mirrored in his activities. Music was his diversion. He spent many hours at the piano and often had the leading members of the Symphony Orchestra at his home. Simple and unassuming, he had a keen sense of humor and a spirit of kindness toward all. We shall long miss his presence at our meetings.

*Fred. J. Taussig, M.D.*

---

### A TRIBUTE

Hugo Ehrenfest was my valued friend and associate in the Editorship of the Journal since its founding in 1920. Among other tasks he developed the important Department of Abstracts and Reviews, and conducted it with unfailing skill because of his wide reading and his knowledge of the world's medical literature.

The many trials and tribulations connected with the editorial conduct of a widely circulated journal with its host of contributors, afforded many occasions on which his advice and suggestions were of utmost value and assistance.

Moreover by his lovable personality, his modesty, his cheerfulness, his always ready spirit of cooperation and his kindly disposition, Dr. Ehrenfest endeared himself to all the members of the Editorial and Publication Staffs of the Journal, who mourn deeply his sudden and untimely death. His many good deeds, his unselfish character, his sympathetic attitude, will all contribute to the happy memories and the esteem in which he was held by his many personal friends and associates. His loss is keenly felt.

*George W. Kosmak, M.D.*

Table II includes all patients whose pulse rate rose to above 110 and whose respiratory rate rose to above 24 during the first stage of labor, and remained so for at least forty-five minutes. This group consists of six Class 3 patients, three Class 2 and one Class 1. A careful review of the histories indicated that two of the Class 2 patients probably should have been diagnosed as Class 3.

Three of the patients developed severe cardiac failure (Class 4) for the first time in their life during the first stage of labor.

TABLE II. PATIENTS WITH PULSE RATE ABOVE 110 PER MINUTE AND RESPIRATORY RATE ABOVE 24 PER MINUTE DURING FIRST STAGE OF LABOR

| CASE | FUNCTIONAL CAPACITY |     |     | DURATION OF LABOR HOURS | PULSE | RESP. | DIGITALIS | DELIVERY | COMMENT                    |
|------|---------------------|-----|-----|-------------------------|-------|-------|-----------|----------|----------------------------|
|      | AP.*                | IP. | PP. |                         |       |       |           |          |                            |
| 1    | 3                   | 4   | 3   | 11                      | 120   | 26    | +         | Forceps  | Failure intra-partum       |
| 2    | 1                   | 4   | 3   | 14                      | 140   | 40    | +         | Forceps  | Failure intra-partum       |
| 3    | 3                   | 3   | 3   | 8                       | 130   | 30    | +         | Forceps  |                            |
| 4    | 2                   | 3   | 3   | 38                      | 120   | 28    | +         | Forceps  |                            |
| 5    | 3                   | 3   | 3   | 11                      | 120   | 30    | +         | Spont.   |                            |
| 6    | 3                   | 3   | 3   | 28                      | 140   | 30    | +         | Cesarean |                            |
| 7    | 3                   | 3   | 4   | 15                      | 120   | 30    | +         | Forceps  | Failure 10 hr. post-partum |
| 8    | 2                   | 3   | 3   | 13                      | 140   | 28    | +         | Breech   |                            |
| 9    | 3                   | 4   | 3   | 31                      | 120   | 40    | +         | Forceps  | Failure intra-partum       |
| 10   | 2                   | 3   | 4   | 44                      | 120   | 28    | 0         | Spont.   | Failure 6 hr. post-partum  |

Figures for pulse and respirations are the maximum rate found for three or more consecutive counts during the first stage of labor.

\*AP., ante partum. IP., intra partum. PP., post partum.

Case 2 had been diagnosed as Class 1 ante partum and had spontaneous rupture of the membranes at home very early in labor, after which she hurriedly dressed, packed, ran down five flights of stairs and came to the hospital in a taxicab. On admission her pulse was 140 and respirations 40. Soon thereafter she began to feel a choking sensation and developed pulmonary edema. She was treated with morphine, atropine, oxygen, and digitalis. Labor continued and she was delivered after a fourteen-hour labor, forceps being used to eliminate the second stage. This patient made an uneventful recovery and left the hospital in such condition that she has subsequently been diagnosed as Class 1 in the cardiac clinic. In her previous pregnancy she had been admitted for rest and digitalization prior to term, was allowed to go into labor spontaneously, and was delivered by forceps at the end of the first stage. During that confinement there was no evidence of severe cardiac failure.

Two patients who had been diagnosed as Class 3 during the last trimester, developed severe failure with basal râles, venous engorgement and cyanosis during the first stage of labor.

ing in Figs. 1 to 5. The chart was continued up to the time of delivery or the onset of any operative procedure which involved the administration of an anesthetic. Analgesia was used as indicated but the barbiturates and scopolamine were avoided because of their tendency to produce restlessness and excitement. Open drop ether or local anesthesia was most commonly used for delivery.

This group of 200 patients included practically all of those with rheumatic heart disease who were delivered during the period when this study was being undertaken. Only a few cases were omitted because of the short duration of the first stage of labor or of the short period of observation in the hospital during this stage, but none of these cases were severe cardiacs. No cesarean section was performed during this period for the primary indication of rheumatic heart disease. Except for one case of pyeloureteritis (Case 8) and one of upper respiratory infection (Case 5), none of the patients included in this study had medical complications apart from the cardiac condition, that is, there was no unexplained fever, thyroid disease, true marked anemia, et cetera.

The various anatomic lesions included in the diagnoses of this group and the ante-partum diagnosis of cardiac functional capacity appear in Table I which also indicates the occurrence of intra-partum and post-partum cardiac failure. As is usual in observing cardiac disease during pregnancy, mitral stenosis is by far the most frequent valvular lesion

TABLE I. ANTE-PARTUM ANATOMIC AND FUNCTIONAL CLASSIFICATION OF CASES

| LESION  | CLASS 1 | CLASS 2 | CLASS 3 | CLASS 4 | TOTAL |
|---|---------|---------|---------|---------|-------|
| MS, MI  | 62      | 84 ●    | 13 ○○   | 2       | 161   |
| MS, MI, AI  | 10 ○    | 17      | 4 ●○    | 0       | 31    |
| MS, MI, AI, AS                                    | 0       | 6       | 0       | 0       | 6     |
| AI, AS  | 0       | 2       | 0       | 0       | 2     |
| Total   | 72      | 109     | 17      | 2       | 200   |
| Incidence of intra-partum and post-partum failure | 1.3%    | 0.9%    | 24%     | 0       |       |

Each case developing failure intra partum ○; post partum ●

both among the group as a whole and among the more serious cases. The relatively large number of Class 2 patients may be accounted for by the fact that the diagnosis was in most instances made during the last trimester of pregnancy. Had the functional classification been made earlier in pregnancy, there might have been more in Class 1 and fewer in the Class 2 group. The incidence of severe failure in the Class 3 group was 24 per cent, but in the other groups was small. This is in accordance with previous experiences<sup>2</sup> which tend to show that patients with Class 1 and 2 functional capacity rarely develop severe failure during pregnancy. The two cases who were Class 4 during pregnancy and yet after treatment improved and went through labor without severe failure, are truly remarkable examples of the possibilities under proper medical management. They are described later in detail.



Two patients without history of previous decompensation developed severe cardiac failure during the first twelve hours post partum.

One of these, Case 7, had been diagnosed Class 3 ante partum as early as the third month of pregnancy. She was given digitalis, followed in the clinic, and admitted ten days prior to the expected date of confinement for rest and further digitalization. Her labor lasted fifteen hours. The pulse was 120 and respirations 28 at the onset, and during the last six hours the pulse was above 120 and the respirations 30. The second stage was eliminated by forceps without excessive blood loss, and she left the operating room in good condition. She continued well until eight hours post partum when she was noted to be pale with a pulse of 140 and respirations of 20. The fundus was still well contracted and there had been no hemorrhage. At that time there were no pulmonary râles, but two hours later she developed pulmonary edema. She responded well to treatment and recovered. The other patient who developed failure post partum, Case 10, had been diagnosed as Class 2 at the sixth month of pregnancy. Her labor lasted forty-four hours without digitalis therapy. After nine hours (thirty-five hours before delivery), the pulse was 120 and respirations 22. After twelve hours the pulse was 100 and respirations 20, after twenty-four hours 110 and 24, after twenty-eight hours 108 and 26, after thirty-six hours 110 and 26, and after thirty-nine hours 120 and 26, respectively. The patient was allowed to continue in the second stage and delivered spontaneously. The pulse finally had risen to 126 and respirations to 30. She had a minimal blood loss and left the delivery room without evidence of pulmonary congestion. Six hours thereafter pulmonary râles, cyanosis, venous engorgement and dyspnea were noted, at which time the pulse was 104 and respirations 28. She responded to treatment, however, and made a satisfactory recovery.

All the remaining patients in Table II received digitalis before or during labor, all but one were delivered by forceps (except one breech presentation) and all did satisfactorily.

TABLE III. PATIENTS WITH PULSE RATE ABOVE 110 PER MINUTE AND RESPIRATORY RATE NOT ABOVE 24 DURING FIRST STAGE OF LABOR

| CASE | FUNCTIONAL CAPACITY |     |     | DURATION OF LABOR HOURS | PULSE | RESP. | DIGITALIS | DELIVERY | COMMENT                |
|------|---------------------|-----|-----|-------------------------|-------|-------|-----------|----------|------------------------|
|      | AP.*                | IP. | PP. |                         |       |       |           |          |                        |
| 11   | 2                   | 2   | 2   | 10                      | 120   | 22    | 0         | Spont.   | Persistent tachycardia |
| 12   | 2                   | 2   | 2   | 27                      | 120   | 20    | 0         | Forceps  | Persistent tachycardia |
| 13   | 3                   | 4   | 3   | 10                      | 120   | 22    | +         | Forceps  | Failure intra partum   |
| 14   | 2                   | 2   | 2   | 9                       | 120   | 24    | 0         | Spont.   | Bearing down early     |
| 15   | 1                   | 1   | 1   | 6                       | 120   | 22    | 0         | Spont.   |                        |
| 16   | 3                   | 3   | 3   | 9                       | 120   | 24    | +         | Forceps  | Bearing down early     |
| 17   | 2                   | 2   | 2   | 10                      | 120   | 24    | 0         | Forceps  |                        |

Figures for pulse and respirations are the maximum rate found for three or more consecutive counts during the first stage of labor.

\*AP., ante partum. IP., intra partum. PP., post partum.

One of these patients, Case 1, had an attack of nocturnal dyspnea at the seventh month of her pregnancy and following this she showed more shortness of breath on exertion than previously and was placed in functional Class 3. She went into labor spontaneously at term. After two hours (nine hours before delivery), the pulse was 120 and respirations 24. Two hours prior to delivery the pulse was 112 and the respirations 26. One-half hour later pulmonary edema developed and was treated with morphine, atropine, digitalis, and oxygen. One hour later the patient was delivered by forceps at the end of the first stage, labor having lasted eleven hours. She made an uneventful recovery. The other patient, Case 9, a part of whose chart is shown as Fig. 1, showed a



Fig. 1.—Case 9, 36-year-old primigravida, Class 3 ante-partum. Pulse (●) and respirations (○) every fifteen minutes during the last six and one-half hours of the first stage of labor at term. Total labor thirty-one hours. Pulse rate 110 and respiratory rate above 24 for twenty-two hours before failure. Developed cardiac failure. Given digitalis and delivered by forceps at full cervical dilatation. Satisfactory recovery. P, pulse; R, respiration.

pulse of 120 to 140 and respirations of 36 to 40 after four hours of labor (twenty-seven hours before delivery). Both rates continued high and after twenty-six hours of labor (five hours before delivery), the patient became restless and developed cyanosis, pulmonary râles, and more marked dyspnea. She was treated as was the previous patient and was delivered at the end of the first stage by midforceps after thirty-one hours of labor. The respiratory rate was increased for twenty-four hours post partum and the pulse for four days, but the patient made a satisfactory recovery.

Another Class 3 patient in this group, Case 6, continued in labor well digitalized for twenty-eight hours, during the last six hours of which both the pulse and respirations were above 110 and 24, respectively. A cesarean section was finally done because of cephalopelvic disproportion. This patient made an uneventful recovery.

TABLE IV. PATIENTS WITH RESPIRATORY RATE ABOVE 24 PER MINUTE AND PULSE RATE NOT ABOVE 110 DURING FIRST STAGE OF LABOR

| CASE | FUNCTIONAL CAPACITY |     |     | DURATION OF LABOR HOURS | PULSE | RESP. | DIGITALIS | DELIVERY | COMMENT                   |
|------|---------------------|-----|-----|-------------------------|-------|-------|-----------|----------|---------------------------|
|      | AP.*                | IP. | PP. |                         |       |       |           |          |                           |
| 18   | 2                   | 2   | 2   | 22                      | 90    | 32    | 0         | Forceps  | Prolonged second stage    |
| 19   | 2                   | 2   | 2   | 8                       | 90    | 30    | 0         | Spont.   | Variable respiratory rate |
| 20   | 1                   | 1   | 1   | 12                      | 80    | 30    | 0         | Spont.   | Bearing down early        |
| 21   | 2                   | 2   | 2   | 15                      | 90    | 30    | 0         | Spont.   | Bearing down early        |
| 22   | 2                   | 2   | 2   | 14                      | 90    | 28    | 0         | Spont.   |                           |
| 23   | 2                   | 2   | 2   | 5                       | 90    | 36    | 0         | Spont.   |                           |
| 24   | 2                   | 2   | 2   | 12                      | 90    | 26    | 0         | Spont.   |                           |
| 25   | 2                   | 2   | 2   | 6                       | 100   | 30    | 0         | Spont.   |                           |
| 26   | 3                   | 3   | 3   | 20                      | 90    | 40    | +         | Forceps  |                           |
| 27   | 2                   | 2   | 2   | 11                      | 80    | 40    | 0         | Spont.   |                           |
| 28   | 2                   | 2   | 2   | 13                      | 80    | 26    | 0         | Forceps  |                           |
| 29   | 2                   | 2   | 2   | 48                      | 106   | 30    | 0         | Forceps  | Prolonged second stage    |

Figures for pulse and respirations are the maximum rate found for three or more consecutive counts during the first stage of labor.

\*AP., ante partum. IP., intra partum. PP., post partum.

first stage of labor. There was no instance of failure in this group of 12 patients.

There was one Class 3 patient, Case 26, whose chart during labor showed a maximum pulse of 90 and respirations of 40 thirteen hours prior to delivery. She received digitalis, was delivered by forceps at full cervical dilatation after twenty hours of labor, and showed no evidence of severe failure. The remaining patients were either Class 1 or 2 and did not receive digitalis. Three were delivered by forceps because of prolonged second stage; the remainder delivered spontaneously. Two of these patients were bearing down early, which may have caused the rapid respirations. One, Case 21, whose chart is shown in Fig. 3, was definitely hysterical with panting type of respirations.

Of the remaining 171 patients of the series none had pulse or respiratory rates above the critical levels during the first stage of labor and no instance of intra-partum or post-partum cardiac failure was encountered. Two of these patients were diagnosed as Class 4 ante partum. Eight were diagnosed Class 3, 92 were Class 2, and 69 were Class 1.

Tables V, VI, and VII pertain to elevation of the pulse and respiratory rates during the second stage of labor. It is evident from examination of these tables that most patients included in the previous tables showing pulse or respiratory elevation during the first stage of labor continued to show this during the second stage. All the new cases in Tables V, VI, and VII were Class 1 or 2 and no serious cardiac failure was encountered in any of these. Seven and one-half per cent of all patients

Table III includes all patients whose pulse rose to over 110 but whose respirations did not exceed 24 during the first stage of labor.

One Class 3 patient, Case 13, who had never previously decompensated, failed intra partum. Her chart is shown as Fig. 2. The pulse was found to be 120 and the respirations 22 after six hours of labor. Two hours later, without change in pulse or respiration, she developed basal râles, venous engorgement, and cyanosis. She improved after receiving morphine, oxygen, and digitalis, and forceps delivery was performed at full cervical dilatation one hour later after ten hours of labor. The post-partum course was satisfactory. The other Class 3

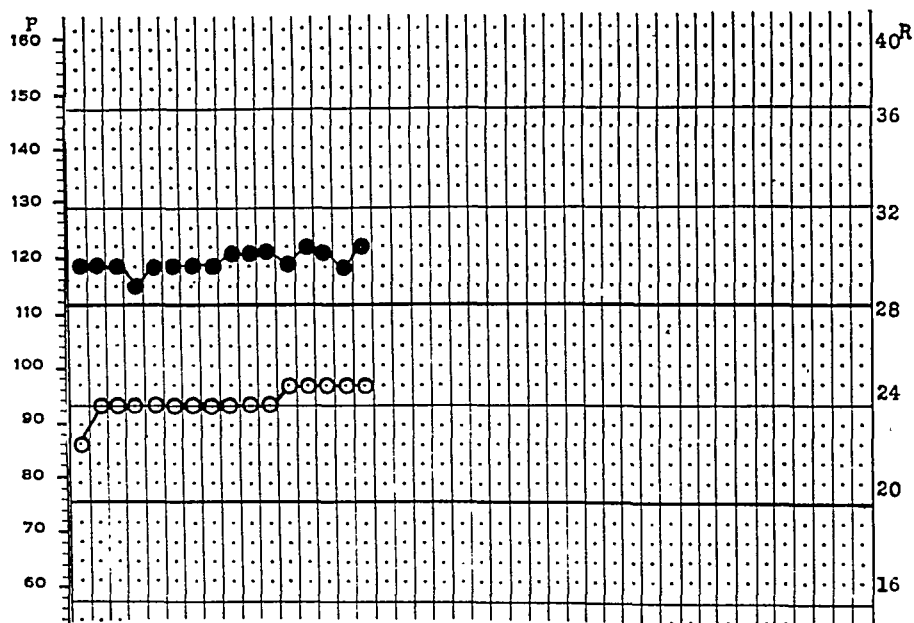


Fig. 2.—Case 13, 25-year-old primigravida, Class 3 ante partum. Pulse (●) and respirations (○) every fifteen minutes during the last four hours of the first stage of labor at term. Total labor ten hours. Earliest recordings two hours before failure show pulse rate above 110, but respiratory rate is not above 24. Developed cardiac failure one hour before delivery. Given digitalis and delivered by forceps at full cervical dilatation. Satisfactory recovery.

patient in Table III, Case 16, showed a pulse of 120 and respirations of 24 eight hours prior to delivery. She received digitalis and was delivered by forceps at full cervical dilatation after a nine-hour labor. The pulse rose to 128 but the respirations did not exceed 24. There was no serious cardiac failure. The remaining patients in this table were either Class 1 or 2. They did not receive digitalis and all came through without serious cardiac difficulty. Two were delivered by forceps and three delivered spontaneously. Two were bearing down early which may have caused the tachycardia. One of the latter patients displayed a persistent unexplained tachycardia in both her pregnancies (Cases 11 and 12). It was considered as probably due to apprehension.

Table IV includes all patients whose respiratory rate rose above 24 per minute but whose pulse rate did not exceed 110 per minute during the

alone. There is a striking similarity between these figures and the percentages obtained in the study of women with normal hearts, as stated in the introductory paragraph.

This series also included the two Class 4 patients previously mentioned who first appeared in the clinic during the seventh month of pregnancy, in a state of severe cardiac failure for the first time in their life history. Both patients improved with bed rest, digitalis, fluid and salt restriction, and continued in the hospital until they went into labor spontaneously, there being no additional obstetric complications. These cases do not appear in the tables of patients with elevated pulse and respirations because the pulse and respiratory counts did not rise above 110 and 24,

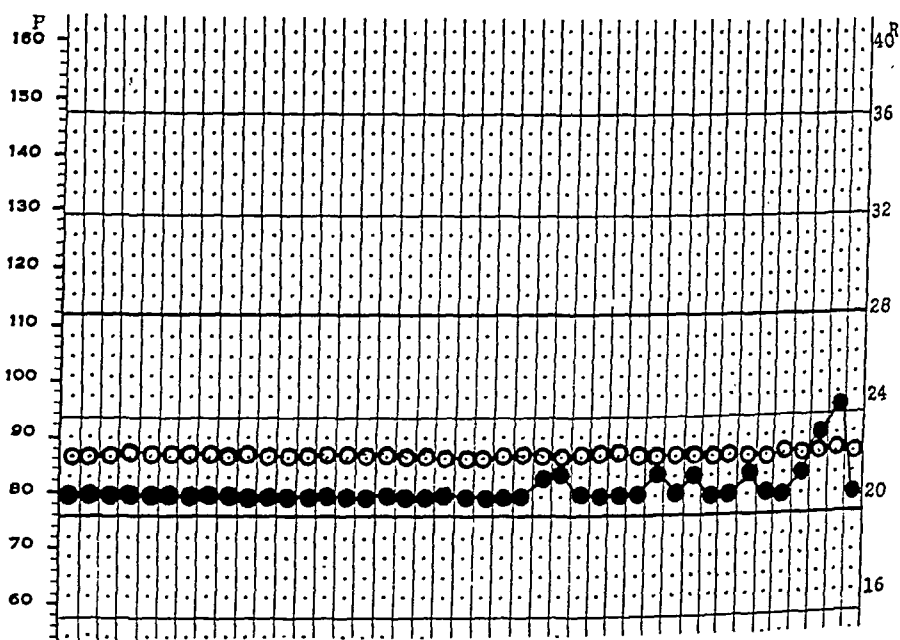


Fig. 5.—Pulse (●) and respirations (○) every fifteen minutes during the last ten and one-half hours of the first stage of labor at term. A 29-year-old primigravida. Class 2 ante partum. Total labor thirty-nine hours. No digitalis, normal spontaneous delivery. No cardiac embarrassment during labor or post partum.

respectively, during labor. Fig. 4 shows the chart of one of these patients who had persistent auricular fibrillation. Forceps delivery was performed at full cervical dilatation in this case and spontaneous delivery occurred soon after full dilatation in the other. The post-partum course was satisfactory in both instances. There were no other instances of ante-partum cardiac failure in the 200 patients studied.

Certain comments seem in order on the duration of labor in these patients. In the 200 cases studied, there were 26 with labor of over thirty hours' duration, the longest eighty-three hours. The pulse and respiratory rates were elevated above the critical levels during the first stage of labor in only 3 of these. Two of them, both Class 3 cases (9 and

showed elevation of both pulse and respirations above the critical levels during the second stage of labor. Six and one-half per cent showed elevation of the pulse alone, and 15 per cent, elevation of the respirations

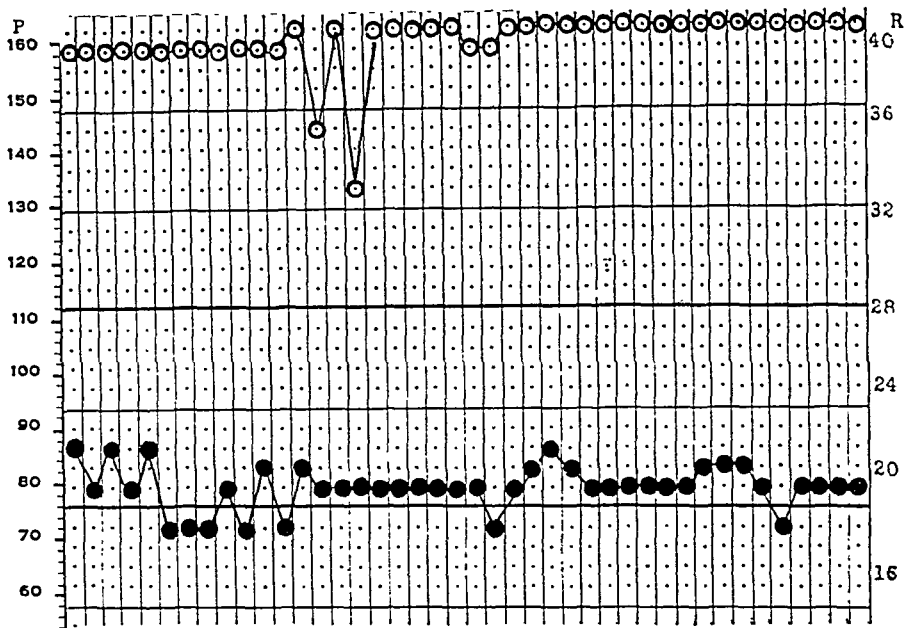


Fig. 3.—Case 27, 31-year-old para iii, gravida iv; Class 2 ante partum. Pulse (●) and respirations (○) every fifteen minutes during the last ten hours of the first stage of labor at term. Total labor eleven hours. Respiratory rate 40 practically throughout labor, although pulse rate was only slightly elevated. No digitalis, normal spontaneous delivery. No cardiac embarrassment during labor or post partum.

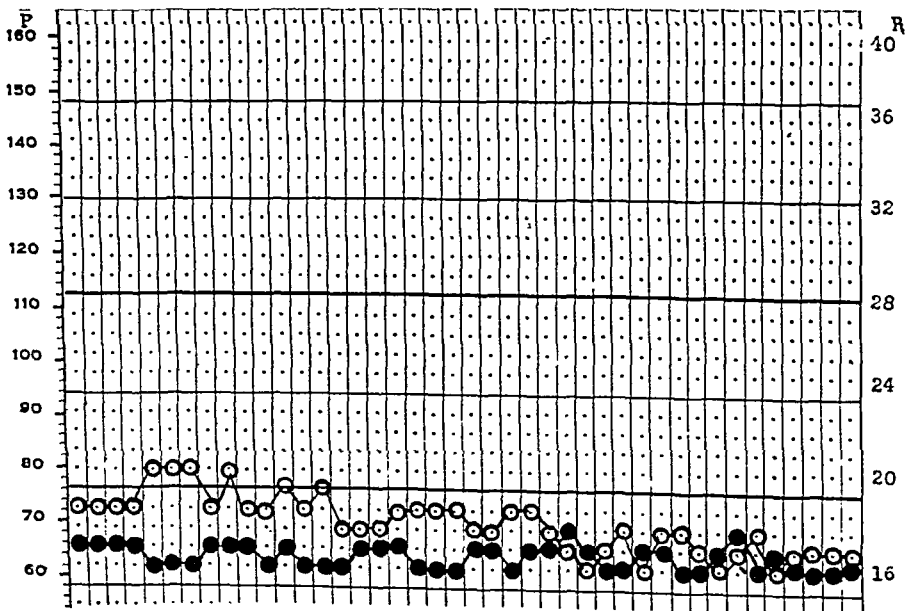


Fig. 4.—Pulse (●) and respirations (○) every fifteen minutes during the last ten and one-half hours of the first stage of labor at term. A 36-year-old primigravida had cardiac failure in the last trimester with recovery. Pulse rate below 110 and respiratory rate below 24 throughout labor. Total labor fifteen hours. Digitalis, forceps delivery at full cervical dilatation. No serious cardiac embarrassment intra partum or post partum.

TABLE VI. PATIENTS WITH PULSE RATE ABOVE 110 PER MINUTE AND RESPIRATORY RATE NOT ABOVE 24 DURING SECOND STAGE OF LABOR

| CASE | FUNCTIONAL CAPACITY |     |     | DURATION OF LABOR<br>HOURS | SECOND STAGE |       | DIGITALIS | DE-LIVERY | FIRST STAGE OF LABOR |       | COMMENT       |
|------|---------------------|-----|-----|----------------------------|--------------|-------|-----------|-----------|----------------------|-------|---------------|
|      | AP.*                | IP. | PP. |                            | PULSE        | RESP. |           |           | PULSE                | RESP. |               |
| 11   | 2                   | 2   | 2   | 10                         | 130          | 20    | 0         | Spont.    | 120                  | 22    | See Table III |
| 12   | 2                   | 2   | 2   | 27                         | 120          | 24    | 0         | Forceps   | 120                  | 20    |               |
| 13   | 3                   | 4   | 3   | 10                         | 120          | 22    | +         | Forceps   | 120                  | 22    |               |
| 16   | 3                   | 3   | 3   | 9                          | 120          | 24    | +         | Forceps   | 120                  | 24    |               |
| 17   | 2                   | 2   | 2   | 10                         | 120          | 24    | 0         | Forceps   | 120                  | 24    |               |
| 36   | 1                   | 1   | 1   | 41                         | 120          | 22    | 0         | Spont.    | 100                  | 22    | See Table III |
| 37   | 1                   | 1   | 1   | 15                         | 130          | 22    | 0         | Spont.    | 102                  | 22    |               |
| 38   | 2                   | 2   | 2   | 22                         | 120          | 24    | 0         | Forceps   | 100                  | 22    | See Table III |
| 39   | 2                   | 2   | 2   | 71                         | 120          | 22    | +         | Forceps   | 80                   | 20    |               |
| 40   | 1                   | 1   | 1   | 21                         | 120          | 24    | 0         | Spont.    | 100                  | 20    |               |
| 41   | 2                   | 2   | 2   | 2                          | 120          | 24    | 0         | Forceps   | 80                   | 20    |               |
| 42   | 2                   | 2   | 2   | 49                         | 130          | 24    | 0         | Forceps   | 100                  | 20    |               |
| 43   | 1                   | 1   | 1   | 39                         | 120          | 24    | 0         | Spont.    | 90                   | 22    |               |

Figures for pulse and respirations are the maximum rate found for three or more consecutive counts.

\*AP., ante partum. IP., intra partum. PP., post partum.

TABLE VII. PATIENTS WITH RESPIRATORY RATE ABOVE 24 PER MINUTE AND PULSE RATE NOT ABOVE 110 DURING SECOND STAGE OF LABOR

| CASE | FUNCTIONAL CAPACITY |     |     | DURATION OF LABOR<br>HOURS | SECOND STAGE |       | DIGITALIS | DE-LIVERY | FIRST STAGE OF LABOR |       | COMMENT      |
|------|---------------------|-----|-----|----------------------------|--------------|-------|-----------|-----------|----------------------|-------|--------------|
|      | AP.*                | IP. | PP. |                            | PULSE        | RESP. |           |           | PULSE                | RESP. |              |
| 18   | 2                   | 2   | 2   | 22                         | 100          | 32    | 0         | Forceps   | 90                   | 32    | See Table IV |
| 19   | 2                   | 2   | 2   | 8                          | 80           | 30    | 0         | Spont.    | 90                   | 30    |              |
| 20   | 1                   | 1   | 1   | 12                         | 90           | 30    | 0         | Spont.    | 80                   | 30    |              |
| 21   | 2                   | 2   | 2   | 15                         | 90           | 34    | 0         | Spont.    | 90                   | 30    |              |
| 22   | 2                   | 2   | 2   | 14                         | 80           | 28    | 0         | Spont.    | 90                   | 28    |              |
| 23   | 2                   | 2   | 2   | 5                          | 90           | 32    | 0         | Spont.    | 90                   | 36    |              |
| 24   | 2                   | 2   | 2   | 12                         | 90           | 26    | 0         | Spont.    | 90                   | 26    |              |
| 25   | 2                   | 2   | 2   | 6                          | 80           | 30    | 0         | Spont.    | 100                  | 30    |              |
| 26   | 3                   | 3   | 3   | 20                         | 100          | 30    | +         | Forceps   | 90                   | 40    |              |
| 27   | 2                   | 2   | 2   | 11                         | 80           | 30    | 0         | Spont.    | 80                   | 40    |              |
| 28   | 2                   | 2   | 2   | 13                         | 80           | 26    | 0         | Forceps   | 80                   | 26    |              |
| 29   | 2                   | 2   | 2   | 48                         | 106          | 30    | 0         | Forceps   | 106                  | 30    |              |
| 44   | 1                   | 1   | 1   | 12                         | 100          | 30    | 0         | Forceps   | 100                  | 20    |              |
| 45   | 1                   | 1   | 1   | 19                         | 110          | 28    | 0         | Forceps   | 80                   | 20    |              |
| 46   | 1                   | 1   | 1   | 50                         | 100          | 28    | 0         | Forceps   | 100                  | 24    |              |
| 47   | 1                   | 1   | 1   | 5                          | 100          | 40    | 0         | Spont.    | 80                   | 24    |              |
| 48   | 2                   | 2   | 2   | 9                          | 110          | 28    | 0         | Forceps   | 80                   | 20    |              |
| 49   | 1                   | 1   | 1   | 10                         | 80           | 30    | 0         | Spont.    | 80                   | 22    |              |
| 50   | 2                   | 2   | 2   | 14                         | 110          | 40    | +         | Spont.    | 90                   | 20    |              |
| 51   | 2                   | 2   | 2   | 5                          | 80           | 30    | 0         | Spont.    | 90                   | 20    |              |
| 52   | 1                   | 1   | 1   | 22                         | 80           | 30    | 0         | Spont.    | 80                   | 20    |              |
| 53   | 1                   | 1   | 1   | 10                         | 80           | 28    | 0         | Spont.    | 80                   | 22    |              |
| 54   | 1                   | 1   | 1   | 11                         | 100          | 28    | 0         | Spont.    | 80                   | 20    |              |
| 55   | 2                   | 2   | 2   | 31                         | 80           | 30    | 0         | Forceps   | 80                   | 22    |              |
| 56   | 1                   | 1   | 1   | 5                          | 100          | 30    | 0         | Spont.    | 100                  | 22    |              |
| 57   | 2                   | 2   | 2   | 30                         | 100          | 30    | 0         | Spont.    | 100                  | 22    |              |
| 58   | 2                   | 2   | 2   | 7                          | 70           | 30    | 0         | Spont.    | 70                   | 20    |              |
| 59   | 2                   | 2   | 2   | 28                         | 90           | 30    | 0         | Forceps   | 90                   | 20    |              |
| 60   | 1                   | 1   | 1   | 42                         | 80           | 30    | 0         | Breech    | 80                   | 20    |              |
| 61   | 1                   | 1   | 1   | 18                         | 100          | 28    | 0         | Forceps   | 100                  | 22    |              |

Figures for pulse and respirations are the maximum rate found for three or more consecutive counts.

\*AP., ante partum. IP., intra partum. PP., post partum.

10), have been previously discussed when considering Table II. The first developed severe failure during the first stage of labor, and the second, six hours after delivery. Both gave early evidence of severe heart strain in the elevation of pulse and respirations. A third patient with prolonged labor, Case 4, also gave early evidence of heart strain by the elevated pulse and respiratory rates. She was digitalized and delivered at full cervical dilatation after thirty-eight hours of labor. She came through without serious failure in spite of the fact that the pulse rose to 120 and the respirations to 28 twenty-four hours before delivery and remained at this level or higher.

Case 29, who was Class 2 ante partum and whose labor lasted forty-eight hours, showed a maximum respiratory rate during the first stage of 30, but the pulse rate was only 106. She did not receive digitalis, and was delivered by forceps after a prolonged second stage without any serious cardiac failure having arisen.

That prolonged labor does not necessarily lead to increased pulse and respirations has been previously demonstrated in normals, but Fig. 5 shows the chart of a Class 2 cardiac patient who delivered spontaneously after a thirty-nine-hour labor without digitalis. The pulse and respirations remained at normal levels and no failure ensued, this being typical of the majority of the 26 cases with prolonged labor.

Table VIII shows the type of delivery and the incidence of digitalis administration according to the various functional classes. The incidence of forceps delivery and digitalis administration naturally increases with decreasing functional capacity.

TABLE V. PATIENTS WITH PULSE RATE ABOVE 110 PER MINUTE AND RESPIRATORY RATE ABOVE 24 PER MINUTE DURING SECOND STAGE OF LABOR

| CASE | FUNCTIONAL CAPACITY |     |     | DURATION OF LABOR HOURS | SECOND STAGE |       | DIGITALIS | DELIVERY | FIRST STAGE OF LABOR |       | COMMENT      |
|------|---------------------|-----|-----|-------------------------|--------------|-------|-----------|----------|----------------------|-------|--------------|
|      | AP.*                | IP. | PP. |                         | PULSE        | RESP. |           |          | PULSE                | RESP. |              |
| 1    | 3                   | 4   | 3   | 11                      | 120          | 40    | +         | Forceps  | 120                  | 26    | See Table II |
| 2    | 1                   | 4   | 3   | 14                      | 140          | 40    | +         | Forceps  | 140                  | 40    | See Table II |
| 3    | 3                   | 3   | 3   | 8                       | 130          | 30    | +         | Forceps  | 130                  | 30    | See Table II |
| 4    | 2                   | 3   | 3   | 38                      | 130          | 38    | +         | Forceps  | 120                  | 28    | See Table II |
| 5    | 3                   | 3   | 3   | 11                      | 120          | 26    | +         | Spont.   | 120                  | 30    | See Table II |
| 7    | 3                   | 3   | 4   | 15                      | 120          | 28    | +         | Forceps  | 120                  | 30    | See Table II |
| 8    | 2                   | 3   | 3   | 13                      | 120          | 28    | +         | Breech   | 140                  | 28    | See Table II |
| 9    | 3                   | 4   | 3   | 31                      | 130          | 40    | +         | Forceps  | 120                  | 40    | See Table II |
| 10   | 2                   | 3   | 4   | 44                      | 120          | 28    | 0         | Spont.   | 120                  | 28    | See Table II |
| 30   | 1                   | 1   | 1   | 6                       | 120          | 30    | 0         | Spont.   | 80                   | 22    |              |
| 31   | 1                   | 1   | 1   | 9                       | 120          | 28    | 0         | Spont.   | 80                   | 18    |              |
| 32   | 2                   | 2   | 2   | 7                       | 120          | 30    | 0         | Spont.   | 80                   | 22    |              |
| 33   | 2                   | 2   | 2   | 9                       | 140          | 28    | 0         | Spont.   | 100                  | 24    |              |
| 34   | 2                   | 2   | 2   | 7                       | 112          | 26    | 0         | Spont.   | 100                  | 24    |              |
| 35   | 2                   | 2   | 2   | 12                      | 120          | 28    | 0         | Spont.   | 100                  | 24    |              |

Figures for pulse and respirations are the maximum rate found for three or more consecutive counts.

\*AP., ante partum. IP., intra partum. PP., post partum.



the second stage by forceps may in many cases help to avoid severe failure. In one of the instances of post-partum failure, Case 10, it seems that the cardiac strain might have been helped by digitalis and severe failure averted by judicious use of forceps. The dystocia labor, however, resolves itself primarily into an obstetric problem and should be treated accordingly as was done in Case 6 in which a cesarean section was performed because of failure of the head to engage.

All but one of these 200 rheumatic cardiac patients were delivered by the vaginal route. Disproportion was present in the patient delivered by cesarean section. There were 2 cases of ante-partum failure, 4 of intra-partum failure, 2 of post-partum failure, and 13 other Class 3 patients, and yet there was not a single maternal death. We would like to think that careful ante-partum care, functional evaluation, study of the pulse and respirations intra partum with appropriate and adequate digitalization, and judicious use of forceps to eliminate the strain of the second stage of labor are the important factors which made these results possible. The question of vaginal versus abdominal delivery in patients with serious rheumatic heart disease will be dealt with in a subsequent paper.

In view of the statement of Hamilton<sup>3</sup> and others that cardiac patients do not fail for the first time during labor, this group showing 4 such cases is of particular interest.

#### SUMMARY AND CONCLUSIONS

Two hundred cases of rheumatic heart disease complicating pregnancy are presented. The ante-partum functional capacity diagnoses were: 72 Class 1; 109 Class 2; 17 Class 3, and 2 class 4. One hundred ninety-nine were delivered by the vaginal route, and one was delivered by cesarean section because of disproportion. Intra-partum or post-partum cardiac failure occurred in 3 per cent of the 200 cases, none of whom had ever previously decompensated. The maternal mortality for the entire series was zero.

Elevation of the pulse rate above 110 per minute with elevation of the respiratory rate above 24 per minute, or such an elevation of the pulse rate alone during the first stage of labor preceded each instance of intra-partum or post-partum cardiac failure by sufficient time to afford a warning of its approach.

Ten patients (5 per cent) had elevation of pulse rate above 110 and respiratory rate above 24 during the first stage of labor. Three of these patients developed severe failure intra partum (Class 1, 3, 3 ante partum) and 2 post partum (Class 2, 3 ante partum).

Seven patients (3.5 per cent) had elevation of the pulse rate above 110 during the first stage of labor with the respiratory rate not above 24. One of these patients developed severe failure intra partum (Class 3 ante partum).

TABLE VIII. THE INCIDENCE OF FORCEPS DELIVERIES AND DIGITALIS ADMINISTRATION IN PATIENTS DIAGNOSED IN THE VARIOUS FUNCTIONAL CLASSES

|                | CLASS 1 | CLASS 2 | CLASS 3 | CLASS 4 |
|----------------|---------|---------|---------|---------|
| Total patients | 72      | 109     | 17      | 2       |
| Forceps        | 8       | 30      | 13      | 1       |
| Digitalis      | 1       | 4       | 17      | 2       |

## DISCUSSION

The pulse was above 110 and the respirations above 24 for more than forty-five minutes during the first stage of labor in all but one of the 6 cases that subsequently developed failure intra partum or post partum. In this case the pulse was persistently above 110 but the respirations were only 22. Five other cases had both the pulse and respirations above the critical figures yet did not develop failure either during or after labor. No significant differences could be found in their antecedent history or in their course during labor to account for this difference in the outcome. A careful review of the pulse and respiratory counts of these patients did not reveal any significant features which might have enabled us to predict that one patient was going to develop severe failure while another one was not. Even so, it seems evident that the presence of high pulse and respiratory counts is to be considered as a warning of impending failure even though this may not develop in all cases. Elevation of pulse alone may have a similar though less threatening significance as only one of 7 cases with this phenomenon developed failure.

We believe that more of these patients might have failed if the appearance of high pulse and respiratory counts had not been considered as a warning of the approach of serious cardiac insufficiency and led to the administration of digitalis and the shortening or elimination of the second stage of labor by the use of forceps. Sustained pulse and respiratory counts above the critical values call for prompt and adequate digitalization unless this has already been effected and for the elimination of the strain of the second stage as soon as feasible by the judicious use of forceps. Where only the pulse or the respiratory rate is abnormally elevated, less importance seems associated with elevation of the respiratory rate alone. No serious difficulty has been encountered in such cases, whereas the occurrence of elevation of the pulse alone preceding failure has been observed. There was no instance of serious cardiac embarrassment when the pulse and respirations remained normal throughout the first stage, regardless of levels attained during the second stage. It is interesting that the incidence of a rise of pulse and respirations above the critical levels during the second stage of labor in cardiac patients so closely parallels that previously observed in normal women. The significance of this is difficult to understand.

The data regarding length of labor suggest that even with an unusually prolonged labor, appropriate digitalization and elimination of

## TRUE BONE FORMATION IN THE FALLOPIAN TUBE

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WHENEVER a tissue is found in an abnormal location, two principal explanations can be considered: *heteroplasia*, i.e., a primary developmental anomaly, due to an error very early in cell division, or *metaplasia*, in the sense that the tissue cells have developed histogenetic potencies, which are not adequate to the particular location (A. Fischel). We know that, a priori, embryonal mesenchymal cells have the faculty to develop into different tissues, like connective tissue, muscle, cartilage, bone, etc. Into which of these the fetal mesenchymal cells develop depends mostly upon the organizing influences of neighboring tissues, particularly epithelium.

The old theory that, wherever bone tissue is found, it must have originated from cartilage or other tissues with normally osteogenic properties, is no longer tenable. Bone may be formed anywhere in the body by metaplasia of ordinary loose connective tissue (Maximow). It has been proved, e.g., that, in certain chronic inflammatory processes, the fibroblasts may acquire an almost embryonic totipotential character. Near deposits of old pus, detritus and calcium salt fibroblasts might develop into osteoblasts.

One may find such metaplastic bone formation as a consequence of chronic inflammation in muscle, heart, blood and lymph vessels, central nervous system and its membranes, lungs, liver and digestive system, urogenital tract, etc. In the Fallopian tubes such an occurrence is extremely rare. Though thousands of extirpated tubes are being examined histologically every year, no report of such a case could be found in a careful review of the American and English literature. Poscharissky,<sup>1</sup> who in 1905 made a survey of several hundred cases of "heteroplastic" bone formation in almost all organ systems, declares specifically that he knows of no such change in the tubes. In looking through old textbooks of pathology, however, I found it mentioned occasionally as a great rarity.<sup>2-4</sup>

The first detailed description of this interesting finding was published by Michaud<sup>5</sup> in 1908. Altogether eleven cases could be found in the world literature, one of which was published by an American author, L. W. Strong, from the Woman's Hospital, New York. But as this case appeared in a German periodical, the subject has as yet not been brought to the attention of the Anglo-American reader. In view of this fact, a brief survey of the cases reported so far is given in Table I.

Twelve patients (6 per cent) had elevation of the respiratory rate above 24 during the first stage of labor with the pulse rate not above 110. None of these patients developed cardiac failure.

No instance of cardiac failure occurred in patients with both pulse and respirations below these critical levels during the first stage of labor regardless of the severity of the cardiac condition as indicated by the ante-partum functional classification.

During the second stage of labor 7.5 per cent of patients had both pulse and respirations above these critical levels, 6.5 per cent the pulse alone, and 15 per cent the respirations alone. No serious significance could be attached to such rises unless they were preceded by similar rises during the first stage of labor, and it is interesting that a similar percentage of normal women have been observed to show these types of pulse and respiratory reaction during the second stage of labor.

Proper management of the cardiac status may avoid severe cardiac failure even in the presence of unusually prolonged first stage of labor.

The successful management of patients with rheumatic heart disease during labor and post partum depends on various factors. Particular consideration should be given to the following:

Careful ante-partum care and cardiac functional evaluation.

Adequate ante-partum digitalization and elimination of the second stage of labor in all Class 3 patients.

Rapid adequate digitalization and elimination of the second stage of labor in any patient whose pulse and respirations exceed the figures which we have considered as a warning of the approach of serious cardiac insufficiency.

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Routine red blood counts and hemoglobin values were determined on 965 pregnant women between the twenty-sixth and the thirty-second week. A red blood count of 3.1 million and above and a hemoglobin of 8.29 Gm. (61 per cent Holden) and higher were taken as within the normal range. It was shown that age and parity have definite and deleterious effects on the blood of pregnant women. The anemia was most marked in the winter months. The morbidity in anemia was found to be lower than in healthy women. Children born of anemic women were found to be heavier. It was noticed that an inadequate ill-balanced diet was found in the cases of anemia.

WILLIAM BERMAN.

My interest in this subject was stimulated by a case operated upon by me in 1927 in the Vienna Lying-in Hospital. As it has not been reported elsewhere I desire to incorporate here some of the photomicrographs from the specimen, because of the highly instructive pictures obtained. The essential features of this case are as follows:

CASE 1.—A 31-year-old nullipara with chronic tuberculosis of the lungs was operated for a pseudointraligamentary cyst of the left ovary, measuring 10 by 8 by 8 cm. The thickened left tube was closely attached to the wall of the cyst and elongated to 13 cm. In its isthmie portion was a hard nodule 7 mm. in diameter and a similar one, measuring 9 mm. was found in the pars ampullaris. The uterus was normal. On the right was a small hydrosalpinx and a cystic ovary.

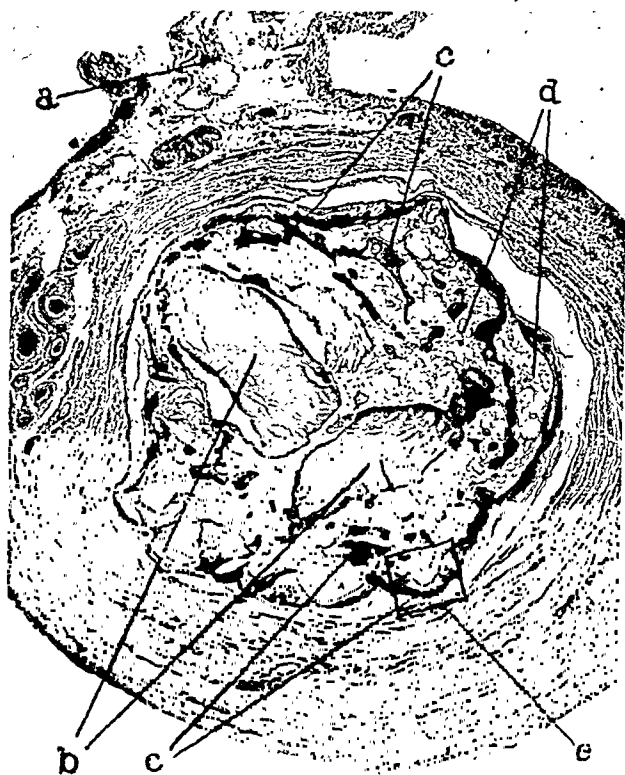


Fig. 1.—Case 1. Pars ampullaris. *a*, Mesosalpinx; *b*, detritus and calcium deposits; *c*, bone trabeculae; *d*, bone marrow; *e*, area of "Fig. 2."

The histologic examination of the left tube shows a most unusual picture (Figs. 1 and 2).

The wall of the pars ampullaris was considerably thickened, the mucosa missing, and the lumen filled by partly calcified bone tissue. The bone trabeculae were arranged irregularly around masses of calcium deposits and detritus. Here and there the trabeculae showed osteoid linings with a few osteoblasts. No signs of osteoclastic resorption could be found anywhere. In between the trabeculae lay bone marrow of which only a small portion looked like typical fat marrow. In most places it was fibrous or of an atrophic, gelatinous character. In the midst of the detritus and also at some places within the bone marrow were

TABLE 1

| NO. | AUTHOR                        | YEAR | AGE | PARA   | MENSES   | PREVIOUS HISTORY  | GYNECOLOGIC FINDINGS                      |                                     |  | LOCALIZATION AND SIZE OF BONE FORMATION                   | PROBABLE ETIOLOGY         |
|-----|-------------------------------|------|-----|--------|--|---|---|-------------------------------------|--|---|---------------------------|
|     |                               |      |     |        |  |   | UTERUS                                    | OVARIES                             | TUBES  |   |                           |
| 1   | Michaud <sup>5</sup>          | 1908 | 21  | Virgin | Primary amenorrhea   | Chlorosis. Hemoptoe at 7 years. Appendectomy at 20 years. | Infantile                                 | Bilateral cystic tumors             | Chronic salpingitis                              | Pars ampullaris on both sides                             | Tuberculosis <sup>9</sup> |
| 2   | Emeljanow <sup>6</sup>        | 1911 | 46  | ?      | ?  | ?   | ?   | Bilateral cystic tumors             | Hydrosalpinx dextra                              | Pars isthmica of right tube. Pea-sized nodule             | Unknown                   |
| 3   | Pozzi and Bender <sup>7</sup> | 1912 | 31  | 0      | Menarche at 17. Menses irregular, scant. Amenorrhea of 4 mo. | Gonitis at 13 years. Ovarian deficiency.                  | Infantile. Pedunculated myoma of egg size | Atrophic tumors                     | Salpingitis nodosa                               | Pars interstitialis                                       | Tuberculosis <sup>9</sup> |
| 4   | Pozzi and Bender <sup>7</sup> | 1912 | 34  | 1      | Menarche at 15   | Irrelevant  | Normal                                    | Small cystic                        | Salpingitis purulenta                            | Pars interstitialis. Hazelnut-sized nodule                | Unknown                   |
| 5   | Strongs                       | 1914 | 30  | 0      | ?  | Irrelevant  | Small                                     | Normal                              | Pyosalpinx tuberculosa                           | Pars ampullaris. Platelet, 1 mm. in longest diameter      | Tuberculosis              |
| 6   | Lehmacher <sup>8</sup>        | 1916 | 47  | Virgin | Regular, scant   | Appendectomy at 41 years                                  | Huge myoma                                | Right: fibroma<br>Left: serous cyst | Elongated to 23 cm.; salpingitis isthmica nodosa | Pars isthmica on both sides. Pea-sized nodules            | Unknown                   |
| 7   | Lehmacher <sup>8</sup>        | 1916 | 56  | ?      | ?  | Chronic cardiac disease                                   | Normal                                    | Senile atrophy                      | Chronic salpingitis                              | Pars ampullaris of left tube                              | Unknown                   |
| 8   | Reichelt <sup>10</sup>        | 1928 | 47  | Virgin | ?  | ?   | Huge myoma                                | Normal                              | Elongated to 10 cm., salpingitis tuberculosa     | Pars ampullaris of right tube. Nodule 1.5 cm. in diameter | Tuberculosis              |
| 9   | Reichelt <sup>10</sup>        | 1928 | 85  | ?      | ?  | ?   | Senile                                    | Senile atrophy                      | Pyosalpinx                                       | Pars ampullaris of both tubes. Nodules 3 cm. in diameter  | Tuberculosis <sup>9</sup> |
| 10  | Bărcă <sup>11</sup>           | 1932 | 47  | 0      | Menarche at 17   | Pulmonary and peritoneal tuberculous                      | Normal                                    | Serous cyst of left ovary           | Salpingitis tuberculosa                          | Left tube pea-sized nodule                                | Tuberculosis              |
| 11  | Foged <sup>12</sup>           | 1941 | 28  | 0      | Menarche at 13   | Osteomyelitis at 2 years                                  | Normal                                    | Serous cysts in both ovaries        | Salpingitis nodosa?                              | Several pea- to almond-sized nodules in both tubes        | Unknown                   |

kinds of calcification which occurred at different times: A primary one in the detritus of the inflammatory process and a secondary one in the reactively formed bone tissue.

As the patient had a tuberculous pulmonary process, a tuberculous etiology of the inflammation had to be considered. There, however, is no evidence for such an origin in the histologic picture.

CASE 2.\*—(Beth Israel Hospital, New York City.) F. G. (Admission No. 32488), a 27-year-old Russian-Jewish, married woman, came to the hospital because of pain in the lower abdomen of several years'

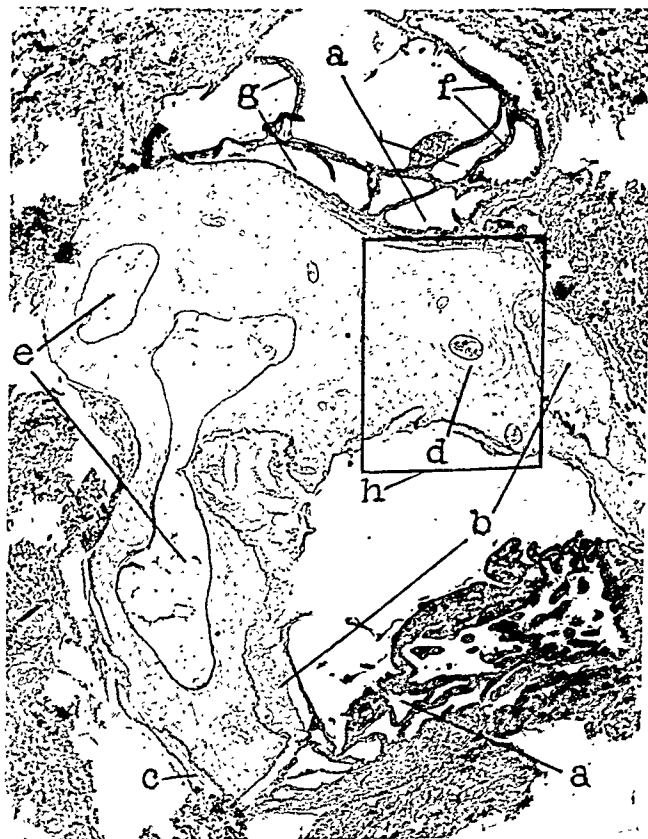


Fig. 3.—Case 2. Pars isthmica. *a*, Tubal folds in pseudofollicular arrangement; *b*, mineral deposits; *c*, osteoid lining; *d*, Haversian system; *e*, bone marrow cavities; *f*, connective tissue of tubal fold; *g*, tubal epithelium; *h*, area of "Fig. 4."

duration, very severe for the past two months. Menstruation had begun at the age of 12 and was always irregular, every thirty-three to thirty-five days, lasting three days; in the past five years only for one to two days, always very scant and painful.

Both parents had tuberculosis. Patient maintained that she had never been ill. She had been married for eight years without ever becoming pregnant.

Medical examination on admission showed nothing unusual.

*Gynecologic Examination.*—Uterus of normal size, anteverted; to the right a cystic adnexal mass, the size of a man's fist. To the left there was a thickened tube and a somewhat enlarged cystic ovary.

\*I am indebted to Dr. H. Lorber for permission to use the clinical data of this case.

isolated amorphous calcified masses. There was also calcification in the surrounding connective tissue. Numerous empty spaces surrounded by foreign body giant cells suggested by their shape that they contained lipid crystals. In the pars isthmica the wall was thickened, the folds were scant, and the mucosa was atrophic. The epithelial lining was fairly well preserved but of more cubic character, only a few remaining folds showed cylindrical epithelium. The lumen was filled with detritus and with numerous cells having round or irregularly shaped nuclei. In one area where a bone hard nodule had fallen out on cutting, many bone trabeculae could be seen; the picture in every respect was identical with the one described above.

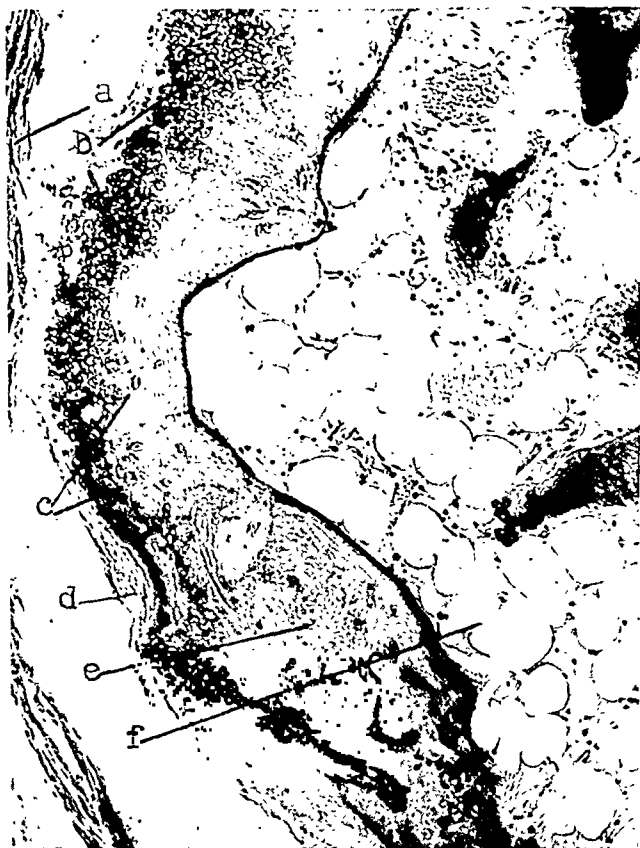


Fig. 2.—Case 1. Area "e" from Fig. 1. *a*, Tube wall; *b*, layer of ossification; *c*, bone corpuscles; *d*, osteoid lining; *e*, bone tissue; *f*, bone marrow.

These histologic findings suggest a chronic indurating salpingitis with local pyosalpinx formation, leading to stenosis and finally atresia of the lumen. In two encapsulated areas, bone formation had taken place. The atrophic, gelatinous bone marrow, the rarity of osteoblastic linings, and the absence of osteoclastic resorption favored the conclusion that the ossification process had come to a standstill. The fact that one could see uncalcified portions in some trabeculae, while on the other hand calcification had occurred not only in conglomerations of old pus but also in the connective tissue protruding into them, in the bony layers surrounding them, and in the hyalinized areas of the eccentric and atrophic tubal wall, makes it probable that we were dealing with two different



by bone tissue. Numerous leucocytes and cast-off cells with small, dark, shrunken nuclei, and the fibrin surrounding them were evidence of an inflammatory process. In some places where the connective tissue bordered on detritus, it formed a narrow, homogeneous, pale-staining band without nuclei. An identical band formed the outer border of the bony structure in many places, and in Azan-stained slides one could ascertain the identity of these structures. The deeper layers of the bone showed the characteristic lamellar arrangement with Haversian canals and cavities that contained fatty bone marrow (Fig. 4). Since there were no osteoblasts or osteoclasts, the process of ossification must have ended long ago.

CASE 3.\*—(Beth Israel Hospital, New York City.) R. F. (Admission No. 44230), a 30-year-old, Polish-Jewish, married woman, came to the hospital because of sterility, pain in the lower abdomen for four years, and an amenorrhea of three months' duration.

Menarche not remembered; menstruation was always irregular, every three to four months, lasting often only one hour, very scant, with mild cramps. This had been assumed to be due to poor ovarian function, and three months prior to admission five stimulative x-ray treatments had been given. As a menstrual interval of three to four months was nothing unusual in this patient, it is not known whether the recent amenorrhea was in any way due to the radiation.

Family history irrelevant.

Patient had typhoid fever as a child. The abdominal pains which started four years prior to admission were attributed to a chronic appendicitis and after two years' observation an appendectomy was performed. The appendix was retrocecal and bound down by dense adhesions. The uterus was infantile and the adnexa normal. This is of interest as it proves that the condition which we are to describe hereafter had developed within the two years between the two operations.

Medical examination on admission showed considerable obesity, probably on an endocrine basis, and a blood pressure of 148/95. The gynecologic findings were: Nulliparous introitus, considerable mucous discharge, a conical cervix in the axis of the vagina, and the uterus in first degree retroversion, normal sized and freely movable. Right adnexa somewhat enlarged and hard. A small dermoid cyst was suspected and an x-ray film made, which showed a "small calcareous circular nodule in the right pelvis at about the location of the right ovary." A Rubin test suggested that both tubes were closed. An attempt at visualization with lipiodol was unsuccessful because the contrast medium permeated into the vessels.

The laparotomy (Dr. I. C. Rubin) showed an infantile uterus. The adnexa were bound down by dense adhesions. Small nodules could be felt in both tubes close to the uterus. On the right was a small tubo-ovarian mass so covered with adhesions that it was impossible to distinguish the outline of the tube, which seemed to be closed in its entire length. The left tube was similarly buried in adhesions and closed. The left ovary contained a small chocolate cyst. The right adnexa, the left tube, and part of the left ovary were removed.

*Histologic Examination.*—The right ovary was transformed into a cystic mass, 5 by 4 by 1.8 cm. The tube, which was closely attached to

\*I am indebted to Dr. I. C. Rubin for permission to use the clinical data of this case.

Laparotomy (Dr. H. Lorber) showed a right parovarian cyst, 4 inches in diameter. The cyst was unilocular and filled with clear serous fluid. The right tube was flattened against the wall of the cyst, and its fimbriated end adherent to the posterior surface of the normal, anteverted uterus. The left tube showed in its middle portion a nodule the size of a cherry. The pars ampullaris was bulbous, closed, and adherent to the lateral pelvic wall and the ovary. The latter contained a cyst the size of a walnut. The retrocecal appendix had a reddened and bulbous tip.

The parovarian cyst, the right tube, the part of the left tube which contained the nodule, the cyst from the left ovary, and the appendix were removed.

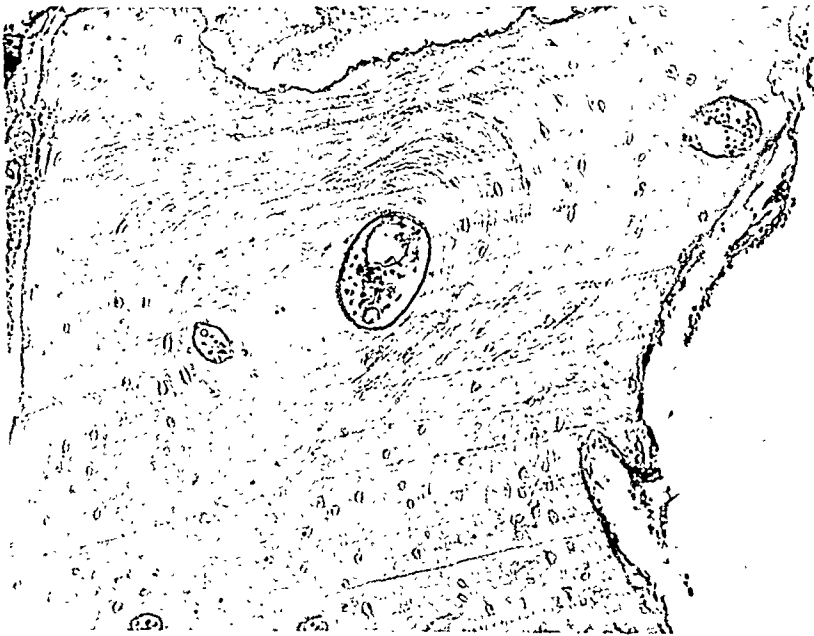


Fig. 4.—Case 2. Area "h" from Fig. 3. Lamellar arrangement of bone tissue around Haversian canal.

Examination showed a papillary, right, parovarian cyst, an elongated otherwise normal right tube, a lutein cyst of the left ovary, and a histologically normal appendix. The removed piece of the left tube was 4 cm. long and contained, in the isthmie part, the nodule described above. While trimming the material we encountered small, hard, yellowish particles near the center of the tube. The specimens had to be decalcified for cutting.

Microscopically one sees that only a few tubal folds have remained, which being fused, present the structure of so-called pseudofollicular salpingitis (Fig. 3). Within the connective tissue of the tubal wall appeared an irregular cavity about 3 mm. in diameter. This cavity communicated in places with the remnants of the original tube lumen, in other places it was separated from it only by the epithelium which appeared lifted off or by epithelium plus a few layers of connective tissue cells. This lumen was filled with granular masses which were surrounded

CASE 4.\*—(Sloane Hospital for Women, New York City.) M. L. (Admission No. 403213), a 37-year-old widowed negress, came to the hospital because of backaches, duration one year, and a growing mass

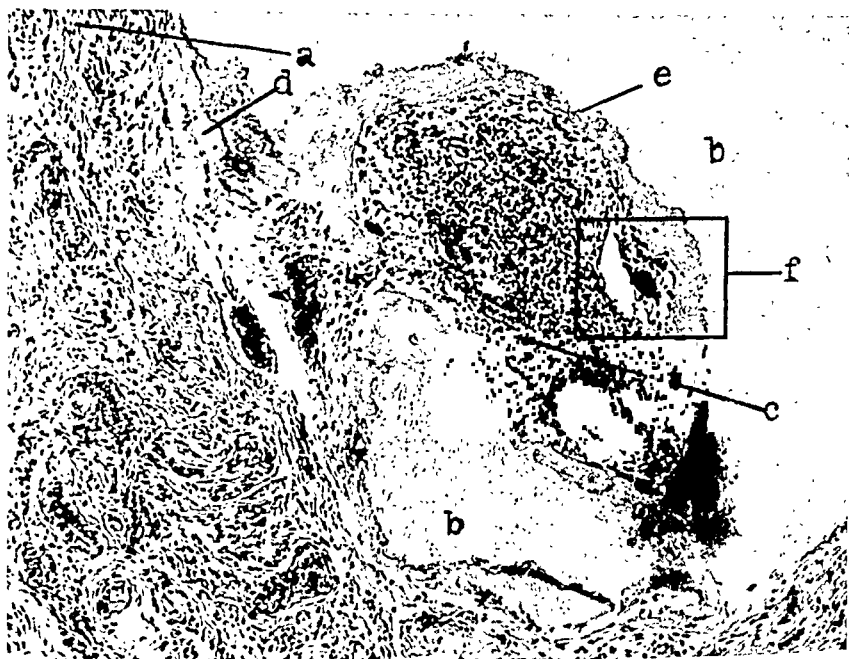


Fig. 5.—Case 3. *a*, Muscular wall; *b*, fibrin and mineral deposits; *c*, granulation tissue; *d*, osteoid tissue; *e*, osteocytes; *f*, area of "Fig. 6."

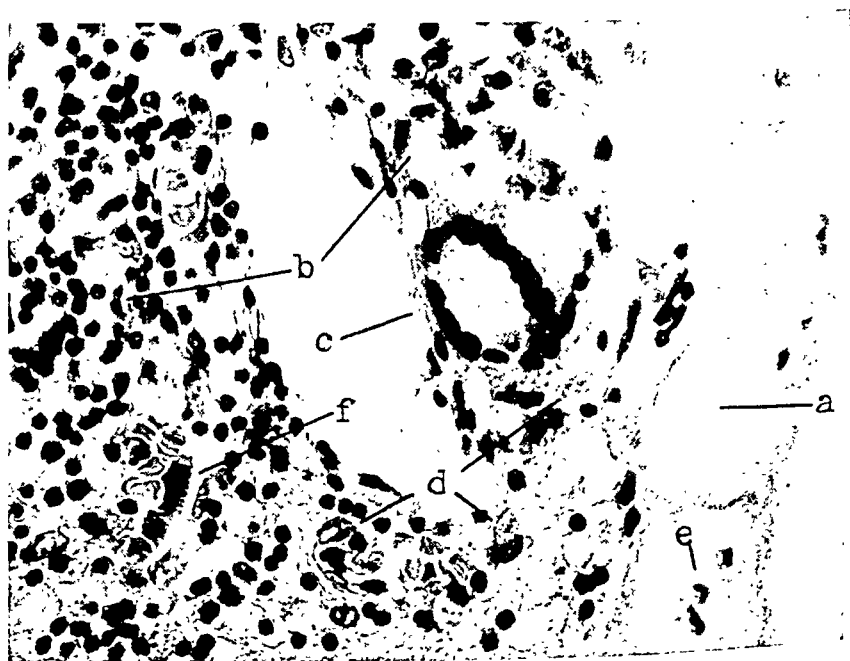


Fig. 6.—Case 3. Area "*f*" from Fig. 5. *a*, Bone tissue; *b*, granulation tissue; *c*, giant cell; *d*, fibroblasts; *e*, bone corpuscles; *f*, capillaries filled with red blood corpuscles.

\*I am indebted to Dr. B. P. Watson for permission to use the clinical data of this case.

the ovary by dense adhesions, measured 5 cm. in length and appeared thin. The fragment of the proximal portion, containing the nodule, had been severed at the time of operation, apparently for inspection, because of its unusually firm consistency. Three centimeters farther distally a similar very hard, small, round resistance could be felt. It could be shifted and when stretching the outer layers of the tube over it, appeared as a yellowish mass. In the pars ampullaris several other such small yellowish masses could be found nearer to the serosal surface. Other irregularly shaped small yellow nodules could be seen on the surface of the ovary.

The specimens from the left ovary and left tube showed nothing unusual microscopically. The right ovary contained many cysts, some luteinic, others lined with layers of granulosa cells, still others only with a single layer of flat cells. The nodules on the surface described above consisted of fibroblasts which partly formed foreign body giant cells. They were grouped around lancet-shaped spaces, which contained highly refractive, colorless, glassy masses. The nodules were surrounded by dense connective tissue.

The right tube was cut partly in serial sections, partly in interrupted serial sections. In the slides from the proximal isthmie part the tubal folds were infiltrated with large mononuclear elements and with a few leucocytes. The epithelium was intact and the outer layers were not inflamed.

In the area of the distal isthmie nodule no lumen surrounded by mucosal folds could be seen. There were only occasional glandlike enclosures, lined with an uncharacteristic flattened epithelium but without communication with each other and surrounded by dense connective tissue. In the midst of this connective tissue there was an irregular space about 2 by 3 mm., filled with pale, red-staining granular detritus. Whether this area corresponded to the former tube lumen or whether it represented a necrotic focus in the tubal wall could not be ascertained. Around this area the connective tissue bundles showed a concentric circular arrangement. Along about one-half of the circumference the bordering connective tissue showed a different character (Fig. 5). Its bundles were coarser, there were fewer nuclei, the intercellular substance becomes wider and homogeneous and finally merges into a red-staining, osteoid anuclear zone. Between this zone and the detritus, a young vascular granulation tissue had grown in, with numerous fibroblasts, which formed a fine meshwork, filled with round cells. One of the serial sections showed an oval giant cell of the Langhans type in the granulation tissue (Fig. 6). The fibroblasts were partly transformed into osteoblasts and formed a shell of true bone tissue around the detritus and small bone trabeculae on the edge of the osteoid tissue. One could see the beginning of lamellar arrangement in the ground substance and the fibroblasts becoming ensheathed by the intercellular substance, taking on the characteristic stellar shape of bone corpuscles. There were very thin layers of bone in some slides, while in others solid lamellar bone structure with perfectly arranged Haversian canals were found. Then the bone became thinner again and disappeared for a few slides completely, only to reappear again in the same manner.\*

\*I wish to thank Dr. A. Plaut, Beth Israel Hospital, New York City, for permission to use the specimens of Cases 2 and 3 from his collection and for his kind help and advice in the description and interpretation of these rare findings.

calcification. Supracervical hysterectomy and bilateral salpingo-oophorectomy were performed.

Pathologic examination of uterus and ovaries showed nothing remarkable. One tube, however, showed a most unusual picture: It was 6 cm. long and its fimbriated end had been incorporated with parts of the adjoining ovary into a stony hard mass, 2 cm. long and 0.75 cm. in diameter.

Microscopically, in the proximal part of the pars ampullaris only slight chronic inflammatory changes could be seen. There was an irregular thickening of the muscular coat with evidence of increased connective tissue. There was increased vascularization of the muscle layers, and

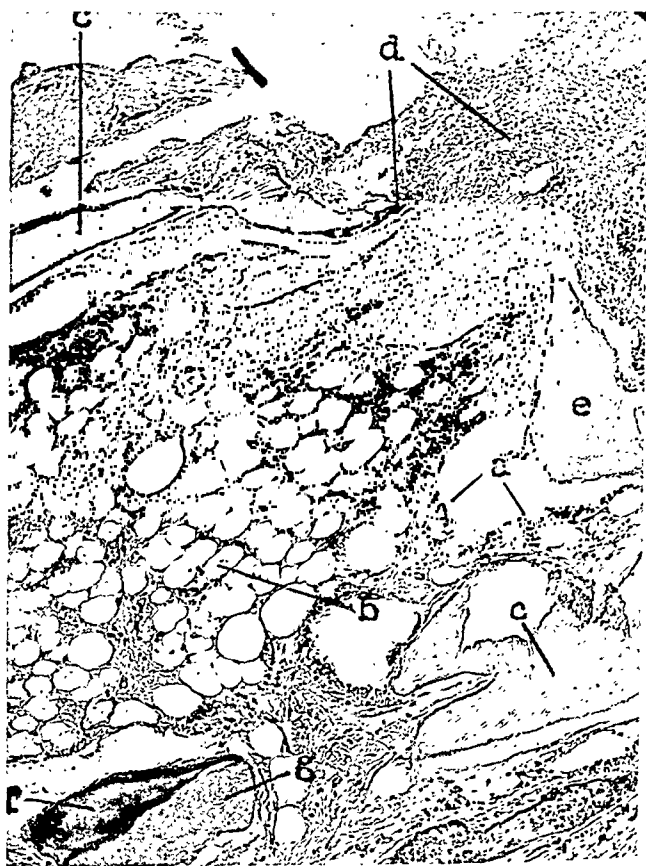


Fig. 8.—Case 4. Pars ampullaris. *a*, Young granulation tissue; *b*, bone marrow; *c*, bone trabeculae; *d*, transition from connective tissue into osteoid zone; *e*, calcium deposit with beginning bone formation on the edges; *f*, calcification in a bone trabecle; *g*, beginning lamellar arrangement, osteocytes.

perivascular infiltrates with lymphocytes and plasma cells could be seen. The tubal folds were elongated and thickened. Infiltrates, similar to the ones described above, were noted perivascularly in the stroma of the folds. The tubal epithelium appeared normal.

Farther distally in the pars ampullaris, the normal structure of the tubal wall had been completely destroyed. Only occasionally could one recognize a few strands of circular or longitudinal muscle bundles. Of the tubal folds one could find only remnants, which had become adherent to each other, presenting the picture of a salpingitis pseudofollicularis.

in the lower abdomen. Menstruation had begun at the age of twelve years and was somewhat irregular, interval about twenty-eight days, duration three days, and always scanty. For the past nine months the amount of flow had been increased.

The patient's husband died from tuberculosis. Family history irrelevant otherwise.

Patient had typhoid fever and malaria at the age of fourteen. In recent years she had repeated attacks of severe tonsillitis. She had bronchopneumonia due to hemolytic streptococci at age of thirty-five.

Medical examination on admission showed old lesions of chorio-retinitis of unknown origin in the left eye. Nothing else of importance.

*Gynecologic Examination.*—Uterus was transformed into a firm irregular mass, reaching two fingers above the umbilicus. Adnexa were not made out. A diagnosis of a large fibroid of the uterus was made.



Fig. 7.—Case 4. Pars ampullaris. *a*, Muscle bundles; *b*, tubal folds in pseudo-follicular arrangement; *c*, well-preserved tubal epithelium; *d*, calcium deposits; *e*, bone tissue; *f*, coarse, dark-staining calcium granula with ingrowing connective tissue; *g*, fibroblasts growing along the mineral deposits.

Laparotomy (Dr. H. Halsted) showed multiple adhesions between the ileum, parietal peritoneum, and the genital organs. There was, at the site of attachment of the ileum to the anterior abdominal wall, a cluster of partially caseous calcified material. This mass was left undisturbed. The uterus contained several large fibroids. There was a chronic salpingitis on one side; the condition of the other tube is not described. One ovary contained a small serous cyst, the other a small abscess with

Here we have a direct metaplasia according to Maximow, analogous to intermembranous bone formation. Finally we have the osseous bars formed around and in the midst of the calcium deposits by osteoblasts, which arise from the fibroblasts of the young granulation tissue. These young cells have much the same properties as the primitive reticular cells of the blood-forming tissues (Maximow). The granulation tissue dissolves and resorbs the mineral deposits and penetrates into the slits thus formed. These cavities become the new bone marrow cavities, and from here the osteoblasts form the bone tissue on the remnants of the detritus and calcified connective tissue.

Further understanding of the processes involved might be gained from animal experiments. Sacerdotti and Frattin<sup>13</sup> were the first who succeeded in obtaining heteroplastic bone formation in tissues which normally have no osteogenic properties. Using the kidneys of rabbits for their experiments they tied the pedicle, leaving only the very limited blood supply from the cortex. After several weeks calcium deposits appeared in the connective tissue beneath the pelvis and after three months a lining of bone tissue formed around the calcified areas. In a few cases a homogeneous osteoid tissue was noted, exactly like that seen in some of our slides. Poscharissky, working with kidneys, obtained the same results. With the liver, spleen, or ovaries, however, complete atrophy without bone formation occurred. This difference in the outcome is due to the blood supply, which the kidney tissue retains from the capsule. These vessels maintain sufficient circulation to prevent necrosis. They also furnish the capillaries for the granulation tissue, which grows into the calcified foci of the kidney medulla. The calcified tissue plays the role of the primordial cartilage. Poscharissky believes that organic substances, remnants of exudate between the calcium salts, furnish the stimulus for the transformation of the fibroblasts into macrophages, which destroy and resorb the calcified tissue, and into osteoblasts which form the new bone tissue. In the bone formations in the lungs one can see coal particles within the osteoblasts, which proves their origin from connective tissue cells.

From these experiments it would seem that an almost complete interruption of circulation is a necessary forerunner of such bone formations. In the tubes, with their excellent blood supply, such an occurrence must of necessity be extremely rare. Extreme elongation and compression by tumors of the uterus or the ovaries and kinking and constriction by dense adhesions were present in at least 10 of the 15 cases. Whether this and the pressure of the detritus masses against the distended tubal walls could have created such a condition of almost, but not quite complete, interruption of circulation as in the animal experiments, we do not know. The fact remains that in thousands of similar cases no bone formation occurred.

In three cases a diagnosis of tuberculosis was made, in three others a tuberculous origin was assumed. One must not forget, however, that,

The tubal epithelium was, on some folds, well preserved; in the dilated pseudofollicles it formed a low cuboidal lining. Most of the tubal wall had been replaced by extensive masses of partially hyalinized fibrotic scar tissue. These masses extended everywhere beneath the mucosa, and thus deformed the wall as well as the lumen. They surrounded huge areas of calcium deposits and detritus, in which numerous lymphocytes and plasma cells could still be recognized.

Partly in the midst of these calcified masses and partly bordering them lay a network of true bone tissue in characteristic trabecular arrangement. Different forms of bone formation could be observed.

Where the connective tissue bundles of the tubal wall ran parallel to the borders of the calcium deposits, their inner layers had become hyalinized. There were fewer and fewer nuclei, and finally there was a homogeneous pale red-staining osteoid zone with gradual transition into bone tissue. In other areas, a young vascular granulation tissue penetrated into the calcium deposits, splitting them up into many islands and forming bone trabeculae on their edges. Where the fibroblasts had become ensheathed in the intercellular substance, they took on the characteristic stellar shape of osteocytes. The spaces between the bone trabeculae were filled with a loose connective tissue containing masses of plasma cells, lymphocytes and monocytes in its meshes. In other areas there was real fatty bone marrow but fully developed myelopoietic tissue could not be found.

The masses of calcium deposits and detritus surrounded and interspersed by hyaline connective tissue and bone trabeculae extended into the broad ligament and to the surface of the ovary. Within the hyalinized connective tissue there were spindle-shaped cracks as sometimes found with old tuberculosis. There was, however, nothing that would prove a tuberculous process. All one can say is, that there was evidence of an old chronic salpingo-oophoritis, probably a tuboovarian abscess, extensive necrosis with subsequent calcification and finally intensive reaction of the surrounding connective tissue with the formation of true bone structure.

#### COMMENT

A completely satisfactory explanation for all pictures encountered is as yet lacking. Cartilage has never been found in any of these cases. There was also never any evidence of relationship to embryonic inclusions or dermoids. One could also think of remnants of an old ectopic pregnancy, but nothing in the case histories, the clinical or histologic findings, supports such an assumption. Older theories like "osteoblast-metastasis" (Klebs) or "embolisms of bone marrow-giant cells" (Jerusalem) may be mentioned as Maximow has proved that such cases do occur. Virchow considered such bone formations to be the end products of a chronic inflammatory process and this theory has been generally accepted since. So far as one can judge from the histologic pictures in the four cases presented in this paper, the bone tissue seems to have formed in three different ways: Where the connective tissue of the tubal wall runs parallel to the bone lamellae, the process resembles periosteal bone formation. In other places one can follow the connective tissue bundles into the periosteal tissue and finally into bone.



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## TRANSPLANTATION OF FASCIA FOR RELIEF OF URINARY STRESS INCONTINENCE\*

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WITHIN less than one hundred years, gynecologists have developed and perfected surgical techniques which can be relied upon to relieve most of the symptoms which are the result of birth injuries to the female sex organs. Factors which contribute to poor results or failures in vaginal plastic surgery include those that arise from:

1. Congenital underdevelopment of the injured structures.
2. Extensive loss of tissue substance resulting from the primary injury or from post-partum infection and tissue necrosis.
3. Increased tissue damage resulting from lack of judgment and skill in applying accepted gynecologic surgical techniques.

Efforts to repair a birth injury are not infrequently handicapped by the results of one or more previous unsuccessful attempts to cure the same condition.

One of the most difficult symptoms to relieve by vaginal plastic surgery is urinary stress incontinence. Statistics prove that 10 to 20 per cent of operations for conditions causing this symptom either fail or are only partially successful. It is with the group of cases in which one or more vaginal plastic operations have failed to cure urinary incontinence that this report is particularly concerned.

Unfortunately, we have not yet acquired either a complete knowledge of the anatomic structures in and about the female urethra or an entirely satisfactory explanation of the physiology of the delicate urethral sphincter mechanism which is responsible for the control of urination.

\*Read at a meeting of the New York Obstetrical Society, March 10, 1942.

for many years giant cells of the Langhans type were erroneously considered absolute proof of tuberculosis. So far as calcium deposits are so frequent in tuberculous inflammations, one could understand some causal relation to ossification, but the frequency of genital tuberculosis and the rarity of bone formation forces us again to assume other coexisting causative conditions. Of what nature these may be we can only guess. Most authors describe the bone formation as a metaplastic process, but we have learned that many pictures which used to be called metaplasia have to be really considered primary tissue malformations. This is particularly true in the female genital tract (R. Meyer). Fischer-Wasels<sup>14</sup> likewise warns against the assumption of a normal potency of the connective tissue to metaplastic bone formation. He maintains that an "inborn disposition," perhaps of endocrine or chemical nature, must be present. In this connection it is interesting to note that so far as one can judge from the case reports, 12 out of the total of 15 patients had an endocrine disturbance (4 certain, 8 probable). It might well be that a combination of the three: tissue malformation plus abnormal chemism plus chronic inflammation or circulatory damage must occur to produce these unusual anatomic changes. Such an assumption of multiple determination would at least explain the rarity of their occurrence.

So far as the nomenclature is concerned, the name "osteoma tubae" used by Emelijanow and also Dietrich<sup>15</sup> in Halban-Seitz's *Handbuch* is a misnomer. As the latter author says very rightly, osteoma means a bony tumor, whereas these formations have no neoplastic character. To speak of metaplastic or heteroplastic bone formation is not justified as both expressions would pretend a knowledge of the histogenesis in these cases which actually we do not possess. These names given by Virchow, backed by his authority and accepted by all authors since, have caused us to be satisfied with an explanation for the bone formation, i.e., metaplasia on an inflammatory basis, which is inadequate. As long, therefore, as the etiology is not clear it is preferable to avoid a definite nomenclature which only tends to obscure the fact that the problem is as yet unsolved.

The condition reported here is, of course, mostly of theoretic interest. The only practical point was brought out by Bârcă and recently by Foged, who found shadows in their x-rays which corresponded to the bone formations. Also in Case 3, as mentioned above, such a shadow was found. It is, therefore, necessary to include the rare possibility of "bone formation in the tube" in the long list of possible interpretations of x-ray shadows in the female pelvis.

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Since 1900, numerous surgical techniques have been described in which transplantation of one of seven different muscles or the round ligaments has been recommended to relieve urinary incontinence. This presentation would hardly be complete without brief comments regarding some of these procedures.

In 1910, Goebell<sup>1</sup> reported on the transplantation of the pyramidalis muscles. In his technique, the muscles were freed except at their attachment to the pubic crest. The free ends were passed backward above the pubic bone and sutured beneath the urethra at its junction with the bladder.

In 1914, Frangenheim<sup>2</sup> modified the Goebell technique by leaving the freed pyramidalis muscles attached to strips of the overlying fascia. These combined strips of muscle and fascia were then placed about the urethra by the same route as described in the original Goebell procedure. Frangenheim also recommended that strips of the rectus abdominis muscles be used when the pyramidalis muscles were found to be poorly developed.

In 1917, Stoeckel<sup>3</sup> recommended that the Goebell-Frangenheim procedure be combined with a vaginal plastic operation with plication of the muscular structures about the vesical neck. This procedure is now referred to as the Stoeckel or Goebell-Frangenheim-Stoeckel technique for urinary incontinence.

In 1907, Giordano<sup>4</sup> described a technique whereby enough of the distal end of the gracilis muscle was dissected free from the inner surface of the thigh to allow it to be transplanted to where it could be wrapped about the urethra and sutured in that position. In 1926, Deming<sup>5</sup> reported an excellent result by use of this method in a case of epispadias.

In 1911, Squier<sup>6</sup> recommended the use of the levator ani muscles. Various methods of using these muscles have been devised. One is to free strips of the mesial margins of these muscles and to suture them together between the urethra and vagina. Another is to detach partially a portion of the mesial border of one of the levator muscles and to transplant it between the urethra and vagina. Attempts have also been made to suture the mesial margins of the levator muscles together in the midline between the urethra and vagina without any detachment of their fibers.

In 1923, Thompson<sup>7</sup> transplanted strips of rectus muscle and fascia downward in front of the pubic bone and sutured them around the urethra and vulva. In 1932, Miller<sup>8</sup> recommended that strips of fascia and the pyramidalis muscles be used in a manner similar to that described by Thompson.

In 1929, Martius<sup>9</sup> described a procedure by which he mobilized the bulbocavernosus muscle and some of its surrounding fatty tissue. This muscle-fat pad was then transplanted between the urethral and vaginal walls.

The purpose in all of these techniques was to prevent the escape of urine by providing external pressure on the urethra as a substitute for the normal sphincter mechanism which had been destroyed or was congenitally absent. Transplantation of muscle is an important feature of every technique with the hope that its contractility will be retained and

Vaginal plastic operations to restore urinary continence invariably include two fundamental objectives:

1. To reduce the caliber of the overstretched lumen of the urethra to what is recognized as normal, including repair of the torn sphincter muscles.
2. To replace the urethra to its normal position beneath the pubic arch and to reconstruct a proper support from the surrounding tissues.

In some patients, in whom both of these objectives appear to have been accomplished, urinary incontinence is not entirely relieved. Some of the failures follow expert vaginal plastic procedures and satisfactory wound healing.

The importance of urinary tract infections as a factor in the etiology of urinary incontinence is well recognized. Elimination of inflammatory lesions of the bladder will stop leakage of urine in some cases in which it seems that vaginal plastic operations have failed. A routine pre-operative investigation of the urinary tract before attempting to relieve urinary incontinence by surgical means might lead to a reduction in unsatisfactory results.

In some instances, the partial successes or failures are probably not due so much to faulty techniques as to the fact that there has been unusual destruction of the urethral sphincter muscles themselves and perhaps of their nerve and blood supply.

In the causation of urinary stress incontinence, the importance of birth injuries to the nervous mechanism which controls bladder function, probably has not received the attention it deserves. In their efforts to cure urinary stress incontinence by vaginal plastic surgery, operators have been accustomed to proceed on the assumption that it is essentially the result of trauma, over-stretching, and permanent relaxation of the urethral sphincter muscles themselves.

Our knowledge of the nerve supply to the bladder and urethra is fairly complete. However, except in cases in which urinary symptoms are caused by spinal cord lesions, we do not yet have the means to be certain that partial loss of urinary control is neurogenic in origin. In other words, we do not have diagnostic methods to determine the extent to which injuries to intrinsic nerves or to nerve endings supplying the urethral sphincter muscles may be responsible for urinary incontinence in any case under investigation. This is unfortunate as there is reason to believe that unrecognized nerve injuries may account for some of our surgical failures. In such circumstances or when the sphincter muscles have undergone too much destruction, complete restoration of function by the usual vaginal plastic procedures can hardly be expected.

With this in mind, various attempts have been made to utilize adjacent anatomic structures with the purpose of providing proper support for the urethra and of developing a substitute muscular sphincterlike action to replace the one that has been lost through birth injury.

2. Restore a displaced urethra to its normal position beneath the pubic arch.

Figs. 2 to 10, inclusive, show the consecutive steps of the new technique which was successfully used to cure urinary incontinence in a woman in whom two previous vaginal plastic operations had failed.

Fig. 2 shows the midline of the anterior vaginal wall being placed under tension with Allis clamps from the external urinary meatus to a point about halfway to the cervix. The dotted line indicates the line of the original incision used to expose the muscular walls of the urethra *U* and bladder *B*, as shown in Fig. 3.

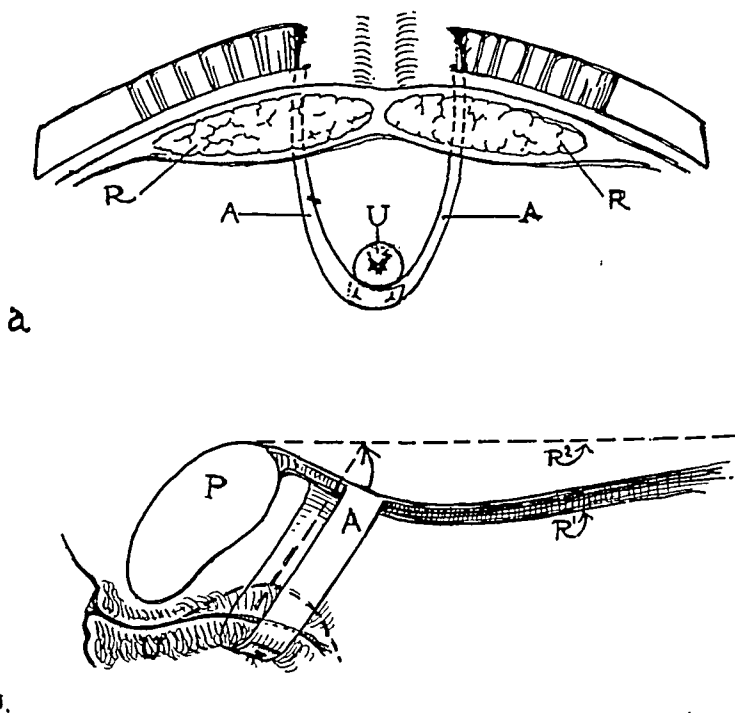


Fig. 1.—*a*, Diagrammatic representation of a technique of transplanting strips of rectus abdominis fascia for cure of urinary incontinence. *A*, Strips of rectus abdominis fascia; *U*, urethra; *R*, recti muscles. *b*, *U*, Urethra; *P*, pubic bone; *A*, rectus abdominis fascial sling; *R*<sup>1</sup>, relaxed position of recti muscles; *R*<sup>2</sup>, position of recti muscles when contracted as with straining.

This incision is carried through the vaginal mucous membrane, the entire thickness of the muscular wall of the vagina including a layer of connective tissue, Fig. 3, *E*<sup>1</sup>, which can be seen as a smooth glistening layer intimately attached to its outer bladder surface. If the incision is carried to this plane of cleavage and the bladder is displaced, it will be noted that on either side of the midline there is another dense layer of connective tissue, Fig. 3, *E*<sup>2</sup>, which is attached to the musculature of the bladder wall, Fig. 3, *B*.

There is still difference of opinion as to the origin of the layers of connective tissue *E*<sup>1</sup> and *E*<sup>2</sup>, but they are probably no more than hypertrophied layers of the connective tissue which act as supporting structures for the muscle fibers of the vaginal and bladder walls. Between the vaginal and bladder walls and extending between the connective tissue layers *E*<sup>1</sup> and *E*<sup>2</sup>, there is another thin layer of loose areolar tissue which is a part of the endopelvic fascia. It is in this layer of loose areolar

sphincterlike action will be developed. From a careful study of all these procedures, it seems unlikely that the pyramidalis, strips of levator or recti muscles, the gracilis or bulbocavernosus muscles can be mobilized and displaced to the positions recommended without almost complete destruction of their nerve and blood supply. In addition to this, there is always uncertainty as to the development of the pyramidalis and bulbocavernosus muscles.

Through experience it has been found that in some cases of stress incontinence of urine, the production of a urethral stricture is sufficient to effect a cure. It seems fairly certain that the good results claimed for all the techniques briefly described above have been attained through improved support for the urethra and partial urethral strictures.

In 1933, Price<sup>10</sup> reported on a technique he used to relieve urinary incontinence in a young woman who had congenital absence of the coccyx and sacrum. Loss of urine was neurogenic and congenital in origin. The procedure that he worked out is of interest, because it incorporates the fundamental principle which has been employed in the new technique that I wish to present. In the technique he used, a strip of fascia lata was passed beneath the urethra by the suprapubic route and the free ends were fixed to the recti muscles 5 cm. above the pubic bone. He had great difficulty in passing the fascia beneath the urethra. Although he accidentally opened the bladder and the wound subsequently became infected, the patient was eventually cured of her urinary incontinence.

#### PROCEDURE

Fig. 1 (*a* and *b*) represents diagrammatically a new surgical procedure for the cure of female stress incontinence of urine. It is like the Stoeckel technique in that it utilizes strips of fascia from the aponeurosis of the oblique muscles of the abdomen which are displaced backward above the pubic bone and sutured beneath the urethra to form a supporting sling. Success of the Stoeckel technique is supposed to depend upon leaving the fascial strips attached to the pyramidalis muscles with the hope that by their contraction the urethra will be compressed thereby preventing the escape of urine from the bladder.

The technique to be described differs from the Stoeckel procedure in that the aponeurotic strips *A* are passed through instead of between the recti muscles *R* at about 4 cm. above the pubic bone *P* (Fig. 1, *a*), before they are sutured to form a sling beneath the urethra *U*. When the abdominal wall is relaxed, it settles backward toward the abdominal cavity. Upon straining, as with lifting, sneezing or coughing, it bulges forward. This has the effect of changing the location of the relaxed recti muscles (Fig. 1, *b*, *R*<sup>1</sup>) to a position represented by the dotted line (Fig. 1, *b*, *R*<sup>2</sup>). This automatically results in a compression of the urethra *U* through the pull of the recti muscles on the fascial sling *A*.

Success of this technique in curing urinary incontinence can probably be increased if it is combined with the usual vaginal plastic steps which are ordinarily employed to:

1. Reduce the caliber of a relaxed urethra to its normal size, including repair of its torn sphincter muscles.

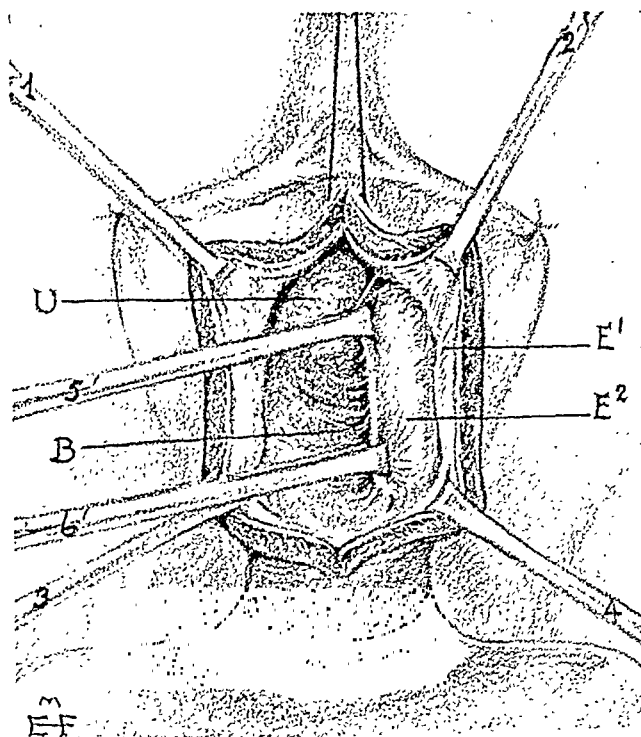


Fig. 4.—Connective tissue layers  $E^1$  on the vaginal wall and  $E^2$  on the bladder wall being held under tension by use of Allis clamps, 2 and 4, and 5 and 6.

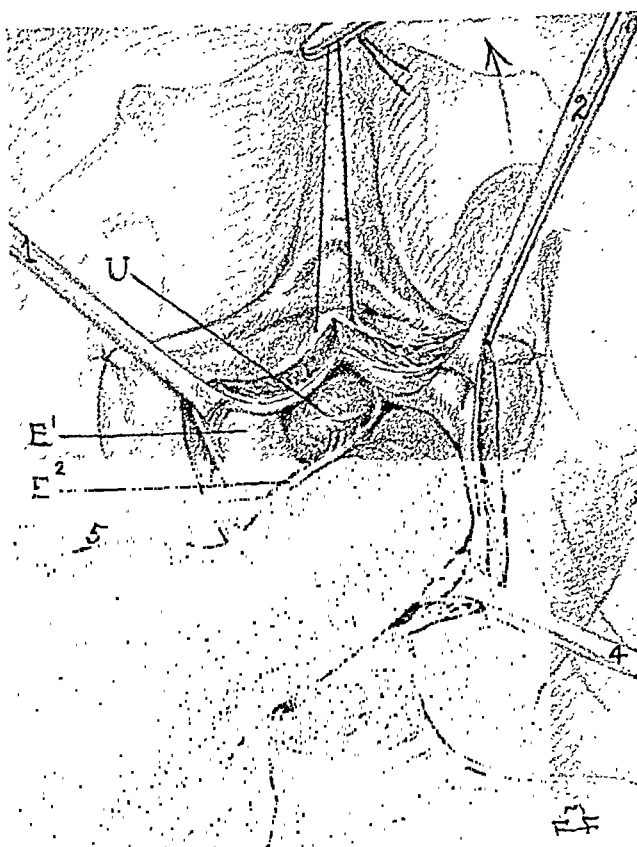


Fig. 5.—By blunt dissection the plane of cleavage between  $E^1$  and  $E^2$ , shown in Fig. 4, has been opened laterally and forward. The finger is being passed through this opening forward and above the pubic bone at the left of the urethra U.

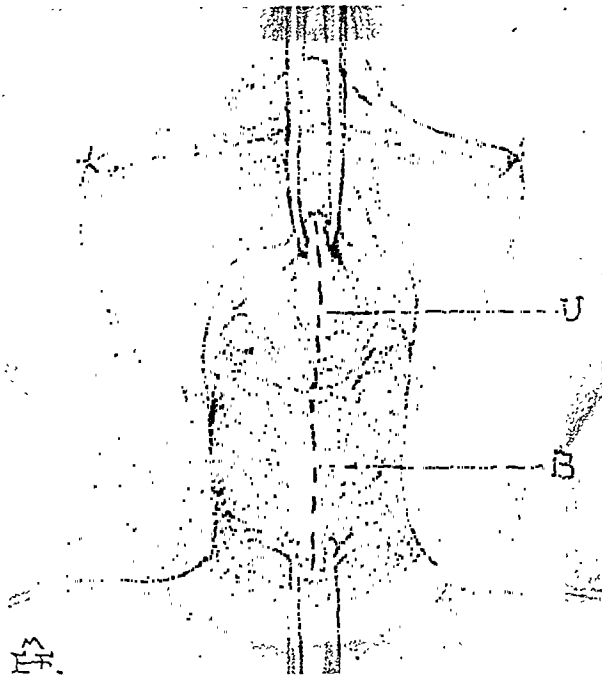


Fig. 2.—Dotted line shows location of original incision in anterior vaginal wall. U, Urethra; B, bladder.

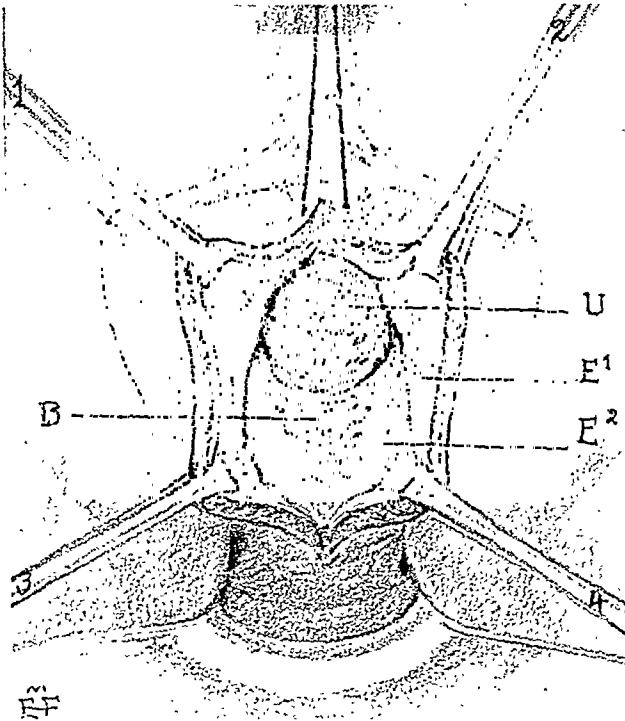


Fig. 3.—Anterior vaginal wall opened exposing the muscular walls of the urethra and bladder. U, Urethra; B, bladder; E¹, connective tissue layer on outer bladder surface of vaginal wall; E², connective tissue layer on bladder wall.



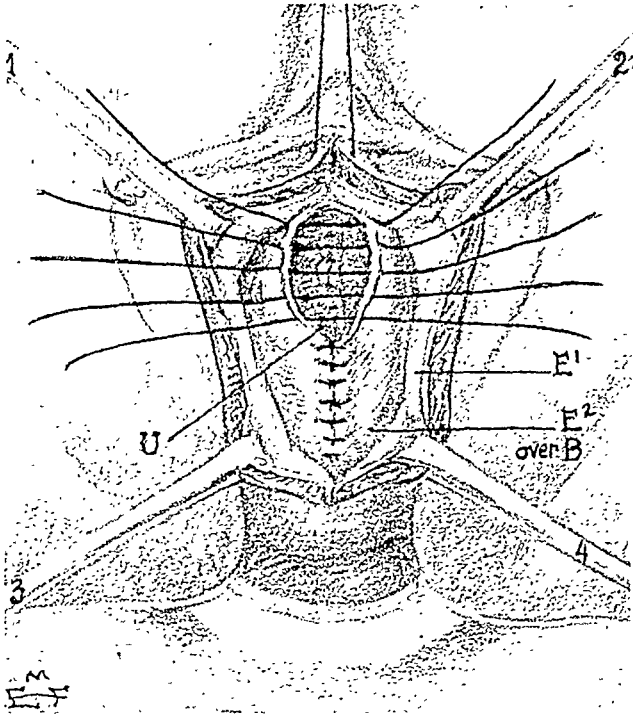


Fig. 7.—Apposition of the mesial margins of the connective tissue layers  $E^2$  is being carried forward over the urethra for additional support.

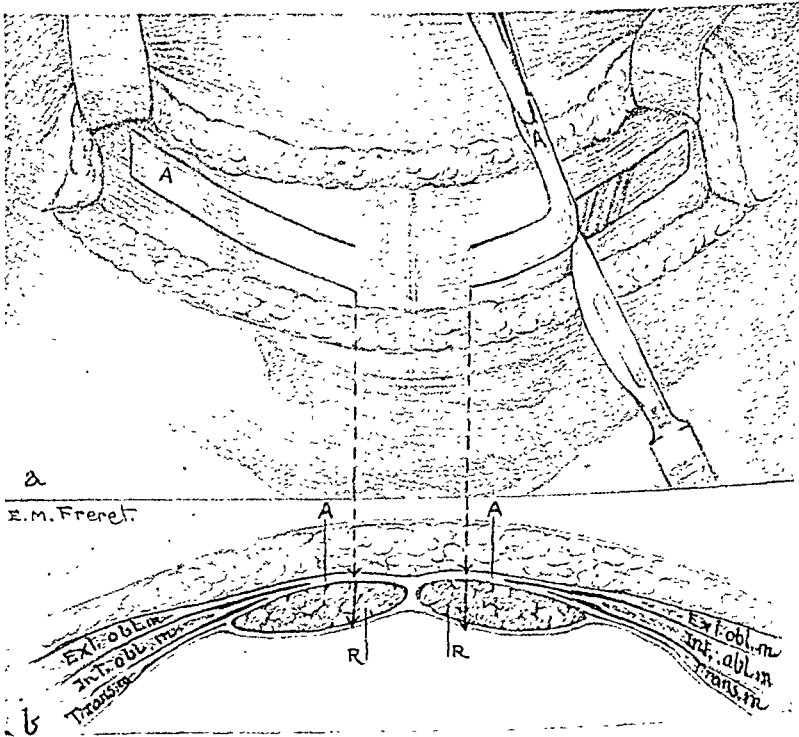


Fig. 8.—*a*, Fascial strips *A* from the aponeurosis of the oblique muscles are being separated through a Pfannenstiel incision. *b*, The dotted lines indicate points about 2 cm. from the mesial margins of the recti muscles *R* through which the fascial strips *A* are passed backward before encircling the urethra.

tissue that practically bloodless blunt dissection can be carried out in every direction. In fact, there is no other natural plane of cleavage in the anterior vaginal wall. Attempts at dissection in any other plane may result in hemorrhage which is troublesome and difficult to control.

By keeping the layers of connective tissue  $E^1$  and  $E^2$  on the bladder and outer surface of the vaginal wall under tension with Allis clamps, 1 and 2 and 5 and 6, as shown in Fig. 4, it is possible by blunt dissection to open an almost bloodless space between  $E^1$  and  $E^2$  which can be extended forward on either side of the urethra.

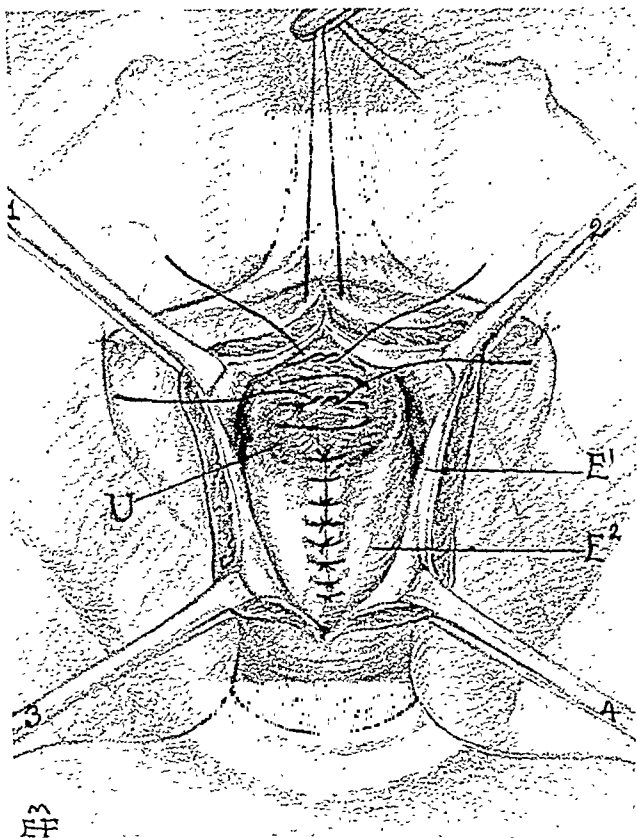


Fig. 6.—The wall of the urethra  $U$  is being infolded with mattress sutures to reduce its caliber and to reunite the torn ends of the sphincter muscles. The mesial margins of the connective tissue layer  $E^2$  on the bladder have been brought into apposition with chromic catgut sutures.

Starting in this plane of cleavage, it is easily possible, as shown in Fig. 5, to pass a finger upward behind and above the pubic bone nearly to the point of attachment of the abdominal muscles to the pubic crest without risk of injury to the bladder or urethra and with very little bleeding.

Fig. 6 shows the lumen of the overstretched urethra being reduced in size by mattress sutures of fine chromic catgut which infold its wall and bring into apposition the torn ends of the urethral sphincter muscles.

Figs. 6 and 7 also show how the thinned-out mesial margins of the connective tissue  $E^2$  on the bladder wall are united in the midline by interrupted sutures of fine chromic catgut to provide additional support for the bladder and urethra.

Fig. 9 shows how clamps 7 and 8 are passed forward above the pubic bone through spaces opened by finger dissection as shown in Fig. 5. Clamp 8 has been forced gently forward through between the fibers of the rectus muscle and is about to pick up the tip of the aponeurotic strip A. By use of clamp 7, the fascial strip has been drawn backward into the vaginal wound. After the fascial strips have been brought into the vaginal wound on either side, they are placed under the urethra as shown in Fig. 10, and are sutured together with sufficient tension to slightly elevate the urethra at about the point at which it connects with the bladder.

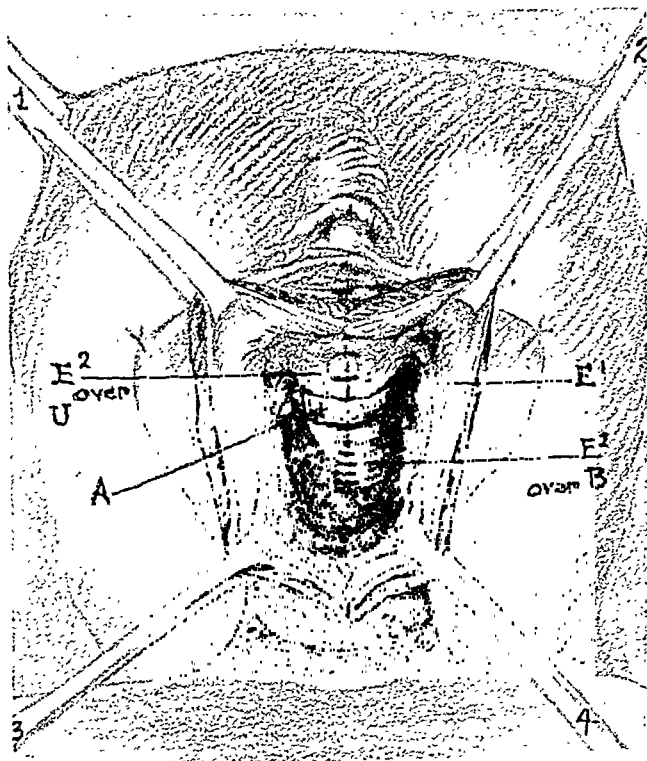


Fig. 10.—The fascial strips A have been united in the midline to form a fascial sling beneath the urethra at its junction with the bladder.

When this has been accomplished any excess tissue is excised from the anterior vaginal wall and the incised margins of the wall are brought into apposition in the midline with interrupted chromic catgut sutures. The abdominal incision is carefully closed in layers to prevent the development of an incisional hernia. Sulfanilamide powder is placed in the abdominal wound, as it is obvious that with this technique there is some risk that infection may be carried into the wound from the vagina.

In the technique as described, aponeurotic fascial strips were developed through a low transverse abdominal incision. If preferred, longitudinal rectus abdominis fascial strips, obtained in the same manner through a low midline incision, may be used. When the opportunity presents itself, it is proposed to try the use of a strip of the fascia lata of the thigh. If this was done, it would seem wise to draw the ends of the strip forward through the vaginal wound and between the fibers of the recti muscles. They could then be united between the recti muscles and

Having completed these steps in the vaginal part of the procedure, the aponeurosis of the oblique muscles of the abdomen is exposed through a Pfannenstiel incision as shown in Fig. 8, *a*.

A strip of the aponeurosis *A*, about 6 cm. in length and 1.5 cm. in width is then dissected free, starting at the outer end on either side and carrying the dissection to within about 2 cm. of the midline where it is

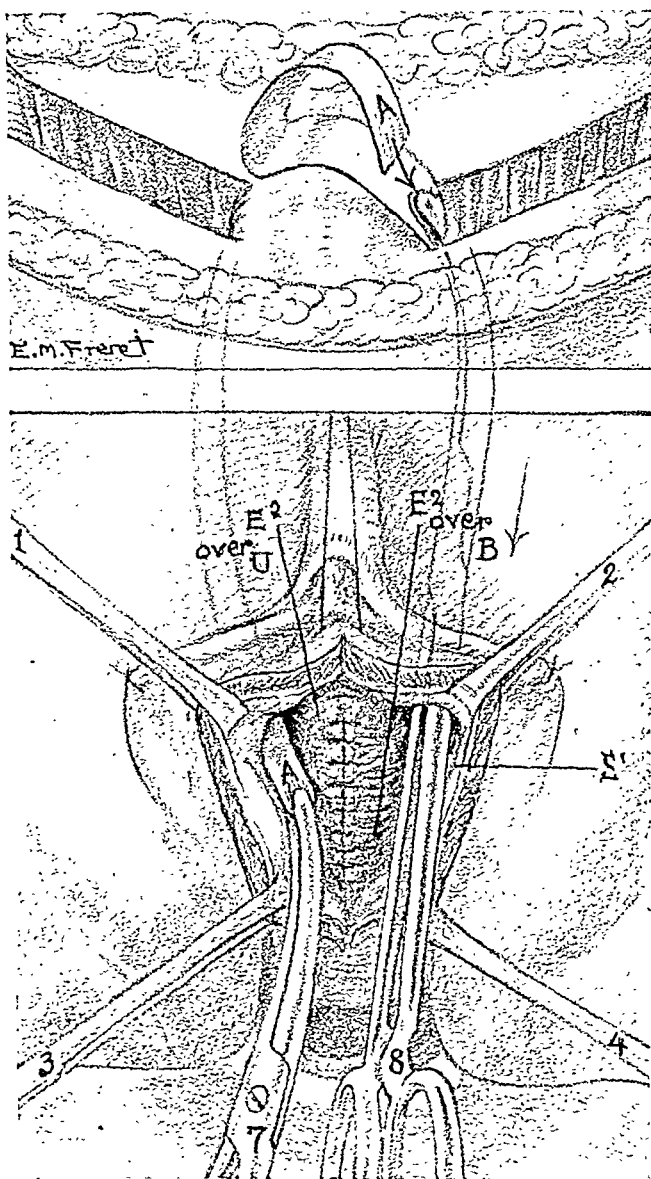


Fig. 9.—Clamps 7 and 8 passed forward in the spaces opened by finger dissection as shown in Fig. 5 are being used to grasp the fascial strips *A* and to draw them into the vaginal wound with one on either side of the urethra.

left attached. The arrows on the dotted lines projected from the attached ends of the aponeurotic strips *A*, to the cross section of the abdominal wall in Fig. 8, *b*, indicate points about 2 cm. from the inner margins of the recti muscles *R*, through which the strips are passed as they are drawn backward along either side of the urethra.

4. It takes advantage of the favorable anatomic relationship of the recti muscles to the urethra. By utilizing the normal variation in position of these muscles, in response to changes in intraabdominal pressure, compression of the urethral lumen is automatically increased at the exact times when it is most necessary in order to prevent leakage of urine.

#### CASE REPORT

The case that I wish to report is that of Mrs. M. McD. (Hospital No. 35233), 53 years of age, and of medium weight and stature. Her past history revealed nothing of importance with the exception of conditions which had occurred incidental to her pregnancies.

During thirty years of her life, she had a rather remarkable experience from the obstetric and gynecologic point of view. Between the ages of 23 and 41 years, a period of 18 years, she had 14 pregnancies. The patient may be excused for loss of memory regarding the details of some of her deliveries, but so far as could be determined from her statements and the available hospital records, the outcome of her pregnancies was as follows:

1. Six full-term pregnancies with one forceps delivery and five spontaneous deliveries.
2. Two premature, spontaneous deliveries at five months' gestation.
3. Five spontaneous abortions.
4. A laparotomy with removal of one tube for ruptured ectopic pregnancy.

The birth weights of 5 of her full-term babies ranged from 8 pounds 11 ounces to 9 pounds 9 ounces.

At 34 years of age, after her fifth full-term pregnancy, she had a vaginal plastic for birth injuries and an operation for retroversion. At 47 years of age, a complete vaginal plastic operation was done at a hospital in Flushing, Long Island. At the same time, the body of the uterus was removed by supravaginal hysterectomy for fibroids. This operation failed to relieve her chief complaint of incontinence of urine.

Four years later, at 51 years of age, another complete vaginal plastic was done at the Woman's Hospital. Following this operation, the anatomic result appeared to be excellent but her most troublesome symptom, incontinence of urine, still persisted.

On June 17, 1941, she was readmitted to the Woman's Hospital for the combined vaginal and abdominal operation described in this report. She was catheterized during the first three postoperative days. From then until her sixteenth postoperative day, when she was discharged, recovery was quite uneventful. She was continent and remarkably free from any bladder symptoms. Now at nearly eight months following this operation, the anatomic result appears to be good. The patient declares that she has had no leakage of urine since the day of her operation and that she is entirely free of any bladder symptoms.

From the patient's statements she had incontinence of urine continuously for 29 years. It began as stress incontinence following delivery of her first baby by forceps at 23 years of age, and finally relieved by the operation described at 52 years of age. Following the birth of her last baby at 37 years of age, she had constant leakage both day and night

its overlying fascia, leaving a loop of fascia as a sling beneath the urethra. Theoretical advantages of using a strip of fascia lata are:

1. It would avoid difficulties encountered in getting fascial strips in patients who have scars of previous abdominal incisions.
2. By avoiding the necessity of excising any abdominal fascia and eliminating the necessity for a rather long abdominal incision, the chances of wound infection and postoperative incisional hernia might be reduced.
3. By use of a fascia stripper, an adequate strip of fascia lata could be obtained through two small skin incisions of the thigh.

#### COMMENT

The new procedure that has been described was devised primarily with the hope of curing post-partum, urinary stress incontinence in women in whom vaginal plastic surgery seemed inadequate. As pointed out, surgical failures by the vaginal route may be due either to excessive damage to the urethral sphincter muscles or possibly to unrecognized injuries to the nervous mechanism which controls the functions of the urethra and bladder. If, by further experience, it can be shown that it is reasonably successful in such cases, it is hoped that the same technique can be used to develop urinary continence in women in whom it is necessary by plastic surgery to construct a urethra. This includes women in whom the urethra is partially or completely absent as a result of congenital malformations or destruction from birth injuries.

The disadvantages of the procedure are that it requires a painstaking technique which should not be undertaken by a surgeon who has not acquired a modern conception of the anatomic structures in the anterior vaginal wall about the urethra and bladder. Dissection in this region is safe and nearly bloodless if carried out in the planes of cleavage described above. If these tissue planes are not followed, blood loss may be excessive and the bladder and urethra may be subjected to serious damage. Difficulties in the dissection are increased by the fact that this technique is particularly suited to patients who have had one or more previous unsuccessful vaginal plastic operations for the same condition. In such circumstances, considerable scar formation is likely to be encountered.

It seems fair to state that the new procedure which has been described has certain advantages over those previously recommended, in that:

1. It utilizes the rectus abdominis muscles which are always well developed and easily accessible.
2. It involves no displacement of the recti muscles or possible loss of function through damage to their nerve or blood supply.
3. It develops a fascial sling in a position and manner which provides additional support and external pressure to the urethra at the point where it is likely to be most effective, i.e., at the junction of the urethra and bladder.

# ADENOMYOSIS OF THE FALLOPIAN TUBE\*

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THE distinctive morphologic characteristic of adenomyosis of the oviduct is the presence within the entire circumference of a thickened segment of myosalpinx of multiple, tubular, small caliber diverticuli of the tubal mucosa. While the process may involve the entire length of the tube, it is usually confined to the most medial segment of the tube. Fixed specimens of oviducts from 87 women who had the disease on one or both sides have been examined during the course of this study, the chief purpose of which is to consider its surgical significance.

Adenomyosis of the tube is an entity distinct from serosal endometriosis, by which term is meant the presence on the pelvic serosa of an endometrial adenosis (endometrium-like mucosal stroma with epithelium of either tubal or uterine type). This study is not concerned with this latter disease. A summary of the differences between the two conditions is presented a few pages hence.

## DESCRIPTION

For 81.4 per cent (S.E.† ± 4.2 per cent) of 86 of the cases studied, the tubules penetrate the entire thickness of one or both myosalpinges (Table I). The epithelium of these glandlike structures is tubal in type

TABLE I. LOCATION OF THE TUBULES OF ADENOMYOSIS TUBAE AS SEEN IN CROSS SECTIONS TAKEN THROUGH THE CENTERS OF INVOLVED SEGMENTS

| LOCATION   | CASES | PER CENT |
|--|-------|----------|
| Pann mural   | 70    | 81.4     |
| 1. Transmural continuity of epithelium of main tubal lumen with overlying serosa (tuboperitoneal fistulas) | 19*   | 22.1*    |
| 2. Subserosal, without apparent serosal continuity   | 51*   | 59.3*    |
| Midmural (inner half of musculature)   | 13    | 15.1     |
| Inner mural (subluminal)   | 3     | 3.5      |
| Total  | 86    | 100      |

\*It is probable that study of serial sections would have augmented these figures appreciably.

for almost all of the specimens studied; rarely is it uterine in type. It usually is ciliated. There is occasionally a single sharp-pointed pro-

\*Abridgment of section on "Adenomyosis tubae" of thesis submitted by Dr. Wrork to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Surgery.

†Standard error, calculated by use of the formula

$$\text{S.E. } (\pm \text{ per cent}) = \sqrt{\frac{A \times (100-A)}{n}} \text{ where}$$

A is the percentage under discussion, and n is the number of cases in that series.

and for this reason rarely left her home. She was unimproved following the two vaginal plastic operations at 47 and 51 years of age, but declares that her last operation was a complete success.

In conclusion it may be stated that:

1. A woman who, through loss of urethral sphincter control, had had partial urinary incontinence for twenty-nine years was cured by a new surgical technique after two vaginal plastic operations for the same condition had failed.

2. The new surgical procedure was devised primarily for the relief of urinary stress incontinence. It may prove to be of value as a step toward developing urinary continence whenever it is necessary by plastic surgery to construct a urethra that is absent as a result of congenital malformations or destructive birth injuries.

3. Ultimate success of the new procedure which has been described must depend upon whether the mechanical and surgical principles involved are sound.

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33 EAST SIXTY-EIGHTH STREET

#### DISCUSSION

DR. THOMAS C. PEIGHTAL.—Dr. Aldridge has devised an admirable means by which the newly constructed periurethral fascia support is re-inforced at the point of greatest strain on the sutures. Thus, for instance, by his rectus fascia sling, the Kennedy operation may be strengthened at the weakest area where the tissues beneath the midurethra most often break down. This is a notable advance in the surgery of stress incontinence and we shall do well to utilize it.

DR. GEORGE F. HOCH.—Dr. Aldridge and I had a patient in common who had two unsuccessful attempts at correction. After the second operation a mass of scar tissue along the urethra acted as a barrier. For a time the result was perfect but soon this tissue disappeared and her incontinence returned. What caused this change? Very likely poor blood supply of this devitalized tissue. The use of live tissue should correct this error.

I believe in all these conditions teamwork between the gynecologist and urologist should decide whether the patient is suffering from an incontinence or an urgency secondary to some urologic disease, before any operative procedure is done. It may prevent some unsuccessful operations.

DR. BENJAMIN P. WATSON.—I am especially interested in the technical aspects of this procedure.

I and some others saw Dr. Miller do one of those fascial support operations, using vertical strips from the two recti muscles; it is quite a formidable procedure. I was impressed by the simplicity of Dr. Aldridge's transverse incision technique, taking two fascial strips laterally from the rectus sheath.



Adenomyosis tubae was found to be bilateral for 83 per cent and unilateral for 17 per cent of 53 cases in which complete pathologic examination of the oviducts was possible (S.E.  $\pm$  5.2 per cent).



Fig. 1.—Cross section through isthmus of oviduct involved by adenomyosis. The irregularity of the muscle and the panmural distribution of the tubules are typical of most such specimens ( $\times 7$ ).



Fig. 2.—Cross section of central portion of oviduct of a single woman, 49 years of age, operated upon because of leiomyoma uteri. Bilaterally symmetrical adenomyotic segments in the tubal isthmuses, bilateral hematosalpinx with endometrium-like stroma beneath a portion of the tubal epithelium. The largest canal is the main tubal canal ( $\times 80$ ).

Another phase of this study is concerned with an endometrium-like mucosal stroma which was found to be associated with adenomyosis tubae for 70 per cent of 81 cases of adenomyosis tubae (S.E.  $\pm$  5 per cent). Among such specimens the tubal type of mucosal stroma predominates,

trusion of the mucosa within the tubule which is without secondary folds; such a structure may represent a rudimentary endosalpingeal plica.

The junctions of these intramural tracts with the main tubal lumen are commonly right-angled. As such a tubule approaches the main tubal lumen, its caliber diminishes and it communicates by means of a narrow neck with the main canal, entering between two of the plicae. Concerning their course through the musculature, Rosenberger<sup>18</sup> has published the only drawing to be found among the previous writings on the subject depicting the course of such tubules as seen in a longitudinal section of an oviduct involved by adenomyosis. Their interlacing course, with occasional enlargements at their infrequent junctions with one another, is illustrated.

Although varying from one to 100 for the oviducts of 82 women, an average of 22 canals per cross section (each tubule cut several times) was found on study of sections taken through the centers of segments involved by adenomyosis.

An excessively thick and irregularly arranged myosalpinx is present in the segment involved by adenomyosis for 89 per cent of 72 of these instances (Table II). The distribution of the size of adenomyotic

TABLE II. MUSCLE COMPONENT OF ADENOMYOSIS TUBAE

| TYPE* | QUANTITY OF MYOSALPINX    | CASES | PER CENT |
|-------|---------------------------|-------|----------|
| 1     | Not perceptibly increased | 8     | 11.1     |
| 2     | Slightly increased        | 19    | 26.4     |
| 3     | Considerably increased    | 41    | 56.9     |
| 4     | Very abundant muscle      | 4     | 5.6      |
|       | Total                     | 72    | 100.0    |

\*Type 1 is properly designated as adenosis; adenomyosis is the most accurate name for the remainder and the best collective name for the group.

TABLE III. SIZE OF THE CLASSIC TYPE OF ADENOMYOTIC NODULES (AT TUBOUTERINE JUNCTION) FOR FORTY-FOUR OF THE FIFTY-FOUR INSTANCES

| SIZE, CM.* | CASES |
|------------|-------|
| 1 by 0.5   | 2     |
| 1 by 0.7   | 7     |
| 1 by 1     | 18    |
| 1.5 by 1   | 11    |
| 2 by 2     | 4     |
| 3 by 2     | 1     |
| 5 by 2     | 1     |
| Total      | 44    |

\*The first figure represents the axial length of the lesion, and the second figure its diameter at the largest point.

nodules is given in Table III. The enlargements of the tube, which are due chiefly to an increase in the muscle component, are often symmetrical, and the process is often bilaterally symmetrical. Usually, although not necessarily, the increase in the quantity of tubal muscle bears a roughly quantitative relation to the number of tubules seen on cross section. Serial sections may demonstrate an isolated tubule in specimens suspected of representing a thickened myosalpinx only, although the thickened muscle may be present alone as a prominent uterine cornu (not a bicornuate uterus). For adenomyotic regions of the tube there is a less distinctive separation of longitudinal and circular muscular lamellae than is normal; in some instances the musculature is grossly irregular (Fig. 1).

obvious near the main tubal lumen than around the intramural adenomyotic tubules. Few of such tubules are found to be cystic, although cystic tubules might be expected to occur commonly if the causative process were inflammation. The narrow necks by which the tubules enter the main lumen cannot be interpreted easily as a formation likely to be the result of inflammation. Adenomyosis tubae is often unilateral in the presence of bilateral salpingitis.

3. Tubal adenomyosis is frequently bilaterally symmetrical. The hypothesis that it is the result of an inflammatory process does not account well for the high incidence of specimens showing similarity of size and position of nodules on the two sides.

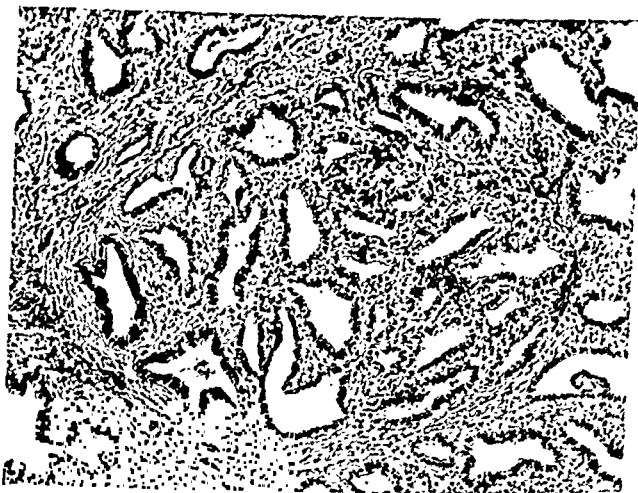


Fig. 3.—Cross section of center of lateral isthmus of an oviduct of a single woman, aged 28 years, operated on because of leiomyoma uteri, showing cribriform or lattice-like lumen of a type herein called congenital rather than adhesive, follicular, or pseudoglandular salpingitis. Elsewhere in such specimens were many regions of panmural adenomyosis. This condition was found alone only once (in control series); in other cases it was found with adenomyosis (present among 23 per cent of 58 cases of adenomyosis in Series 1 and 2). It was found among only two of the specimens showing both adenomyosis and tubal pregnancy. Tubal epithelium and tubal stroma were present throughout ( $\times 105$ ).

4. There are more tubal anomalies among a series of specimens of adenomyosis tubae than among a comparable series showing evidences of chronic salpingitis. In 23 per cent of the 58 cases comprising Adenomyosis Series 1 and 2, a cribriform endosalpinx of the type shown in Fig. 3 was present. Segmental agenesis of the endosalpinx was present for 4, segmentally miniature lumen (a seventh of the normal diameter) for 1, and diffuse adenomyosis without a main tubal lumen for 6 of the specimens among these 58 cases. In all, in 41 per cent of 58 cases of adenomyosis tubae there was some other developmental anomaly of the tube on one or both sides (S.E.  $\pm 6.5$  per cent).

5. Unilateral adenomyosis tubae frequently is accompanied by homolateral adenomyosis uteri; the frequency of this concurrence has not been established. This situation suggests that there may be a predominant involvement of one of the two Muellerian canals of one person by the

the endometrium-like endosalpinx being present focally throughout them; it more often surrounds the epithelium of the tubules than it does that of the main tubal canal (Fig. 2). The question whether this condition adenomyosis, or their concurrence possesses the greatest significance has not been settled.

#### ORIGIN

There are three principal hypotheses of the origin of internal Muellerian adenomyosis: (1) that it is the result of inflammation, (2) that it is congenital, and (3) that it represents a blastoid growth of epithelium from a normally placed Muellerian mucosa.

Dougal<sup>3</sup> stated that adenomyosis tubae was known as an entity for at least fifty years before the contribution of von Recklinghausen<sup>17</sup>; however, little interest was shown in the condition until the appearance of the latter's monograph in 1896. He was reminded of the mesonephron by these structures, believing that some of them represented Henle's loops and glomeruli. He called such fusiform enlargements of the medial isthmus "tubal angle adenomas" (Wolffian). Pick, Kossman and Lockstedt (quoted by Villard and others<sup>21</sup>) lent their support to the belief that the tubules arose from the Wolffian body. By means of an embryologic approach, Meyer demonstrated this hypothesis to be untenable.

Chiari,<sup>1, 2</sup> one of the first to write on the subject, contributed the term, "salpingitis isthmica nodosa," which is used occasionally today. As his term implies, he considered the condition to be the result of foregoing salpingitis. After this idea had fallen into the discard during the years following Chiari's publication, von Franque (quoted by Dougal<sup>3</sup>) revived the hypothesis of an inflammatory genesis for adenomyosis of the tube. Meyer, the most able protagonist of this concept, stated his belief that the downgrowth of tubal mucosa was the result of hormonal and inflammatory stimulation, and that the increase in the muscular component of the structure was a form of hyperplasia in consequence of irritation about the penetrating growth of the tubules. Villard and others supported this view. In all, many contributions have been made, few in English.

Supporting the hypothesis of congenital origin, Schridde and Schoenholz, Lahm,<sup>10, 11</sup> Mestitz, and Weyeneth have made outstanding contributions. The last mentioned expressed his disagreement with Meyer's belief that adenomyosis tubae does not occur among newborn girls. Solutions for these problems, which require microscopic study of serial sections on a large scale, have not been settled yet unequivocally. Hoehne and Lehwirth have also made extensive studies on the subject.

In favor of the developmental (either congenital or postnatal), and opposed to the inflammatory genesis of adenomyosis tubae, the following evidence is available:

1. Adenomyosis is more common at the uterine ends of the oviduct, which inflammation touches lightly, than at the ampullar portion where the residue of inflammation is prominent.

2. There is no scar tissue to be seen around the usual adenomyotic tubule. When there has been previous salpingitis, its residue is more

not denied that such could occur; however, such an occurrence must be very uncommon indeed.

It is probable that the uterine mucosa and the juxtauterine endosalpinx (the middle Muellerian segment being the most highly differentiated portion of the tract) not only are more likely to be the sites of anomalies, but have a greater capacity than the upper and lower parts of the tract to react to any type of stimulation (physical, hormonal or inflammatory) by downgrowth of tubules. It is true that adenosis of the vagina and of the upper reaches of the oviduct is much less frequent than is the disease in the middle segment of the Muellerian tract.

#### DIFFERENTIATION OF "INTERNAL" AND "EXTERNAL" ADENOMYOSIS

The lesion under discussion here is the so-called "internal" type of Muellerian adenomyosis. By the "external" type generally is meant the presence in or on the pelvic serosa or other extragenital sites of regions of Muellerian mucosa. This is more properly a form of adenosis, since there is rarely any muscle growing with the ectopic endometrium-like tissue. Reference may be had to Table IV for other points of differentiation.

TABLE IV. DIFFERENCES BETWEEN ADENOMYOSIS TUBAE AND SEROSAL ENDOMETRIOSIS

| DIFFERENCES                               | ADENOMYOSIS TUBAE   | SEROSAL ENDOMETRIOSIS   |
|---|---|---|
| Synonyms found in study of the literature | Internal adenomyosis, internal endometriosis, endosalpingosis   | External endometriosis, external adenomyosis, adenosis  |
| Epithelium of tubules                     | Usually tubal type<br>In continuity with mucosa of main tubal lumen; occasionally with overlying serosa | Tubal or uterine<br>Not in continuity with mucosa of main tubal lumen; closed or open to serosa |
| Length of tubules                         | Traverse radius of tube for 81 per cent of cases  | Short or nonexistent  |
| Location of tubules                       | Intramuscular<br>Tubules mainly submucosal  | May invade muscle for short distance; not often on tubes<br>Mainly subserosal or serosal        |
| Mucosal stroma                            | Chiefly tubal type  | Usually uterine type  |
| Muscle component                          | Excessive and irregular   | Absent; adenosis only   |
| Patency of ostium                         | Closed more often   | Almost always open  |
| Dysmenorrhea                              | Rare  | Practically always present  |

tion between the two conditions. Several instances wherein the two conditions existed concurrently have been encountered at the Mayo Clinic, in which instances it is possible that the serosal disease represented a transmyosalpingeal extension of the adenomyosis. Endometrium-like endosalpinx was present focally beneath the tubal epithelium of the "internal" tubules within these specimens. This will be discussed elsewhere.

Some writers group adenomyosis and serosal endometriosis together under one heading, referring to them collectively as "ectopic endo-

process. Weyeneth first recorded an observation of this feature of the disease, and several such observations were made during the course of the present study.

6. Adenomyosis has a predilection for the tubouterine junctional zone of the Muellerian tract, just as other anomalies of the body (such as those of the enteron) have a predilection for transitional segments. Its incidence is thought to diminish caudad and craniad from the tubouterine junctional zone.

Sampson made a significant contribution to the study of the genesis of some types of adenomyosis tubae, as well as of serosal endometriosis. By means of studies of tubal stumps after salpingectomy he demonstrated that new tubules had grown from the previously ligated tubal mucosa ("endosalpingosis") among 76 per cent of 147 tubal stumps, whereas growth of new tubules was present among only 8 per cent of a control series of 200 specimens. As he indicated, this is excellent evidence that some of these lesions found in tubes not previously operated on may be acquired during adult life. Among the 118 control cases reported herein (194 oviducts) in 9 cases, or 7.6 per cent, adenomyotic regions were found on one or both sides. Sampson found, not only that the new growth of tubules from the tubal stump penetrated the adjacent myosalpinx, but that in some instances penetration of the overlying serosa occurred with involvement of the bowel (6 cases), the ovary (4 cases), or the abdominal wall after ventrifixation of the uterus (3 cases). For 2 specimens he found tubal pregnancy within the tubal stump, the result of canalization incident to the penetrating growth of the tubules. Since inflammation was present among 18 of the specimens studied by him, he interpreted the mucosal proliferation as probably having been initiated by inflammation and by the trauma incident to the salpingectomy.

The proximity of the most medial segment of the tube to the most rapidly regenerating tissue in the female body (endometrium during sexual maturity) suggests that the penetrating growth of adenomyotic tubules may be akin to the rapid regeneration of the mucosa of this adjacent segment.

There may be a relation between the absence of a muscularis mucosae and submucosae in the Muellerian tract, and the development of adenomyosis. In many regions throughout the oviduct the epithelium lies practically in contact with the myosalpinx, the lamina propria of the mucosa being extremely thin. A process similar to adenomyosis rarely if ever occurs among those hollow viscera having such layers intervening between muscle and mucosa.

In summary of this section it may be said that some instances of adenomyosis tubae are congenital, while others are acquired during adult life, and that the histologic characteristics of the lesion do not resemble those of lesions known to be the result of inflammation. During the course of this study no specimen was encountered which presented the characteristics usually associated with a postinflammatory picture. It is

rather than of Wolffian origin. Certainly in many instances it is only by means of microscopic study of serial sections that one can distinguish between the two types of tubules.

For two oviducts nodules measuring 2 by 2 by 2 cm. have been found at the ampullar ends (Fig. 4). At the uterine extremities of both of these two specimens there was panmural adenomyosis. Both of these large nodules were filled with clotted blood and in each instance the cavity of the mass was in continuity with that of the tube. Such structures are commonly called "adenomyomas" although they do not have



Fig. 4.—Dorsum of uterus of a 59-year-old woman operated upon because of carcinoma of the endometrium. Right purulent salpingitis. The diameter of the uniformly thickened tube on the right is 8 mm., while that of the isthmus of the left is 5 mm. Diffuse adenomyosis throughout the right tube. The lumen of the mass measuring 2 by 2 by 2 cm. at the ovarian end of the right tube is in continuity with the main tubal lumen. One of the fimbriae may be seen at the lower pole of the mass. This sac contained clotted blood.

the structure of a true neoplasm. The mucosa within these two enlargements was for the most part absent, probably as the result of pressure necrosis. The wall of each, composed of heavy scar tissue, is a formation not seen among specimens of tubal pregnancy. They undoubtedly represent manifestations of the same process present at the medial ends of each of these two oviducts, similar to rectovagino-septal "adenomyoma."

#### COLLECTION AND RECOGNITION OF SPECIMENS OF ADENOMYOSIS TUBAE

Table V shows the methods of selection of the several series of cases studied, and Table VI lists the primary reasons for operation among 87 patients who had adenomyosis tubae. Adenomyosis was present

metrium," "Muellerianosis," "adenomyosis" or "endometriosis." This no longer seems warranted in view of their entirely separate nature and significance.

#### PATHOLOGIC DIFFERENTIAL DIAGNOSIS OF ADENOMYOSIS TUBAE

Oviducts that are the site of chronic salpingitis may be so amazingly tortuous that an accurate cross section is difficult to secure. Cross sections of such specimens frequently cut through parts of the lumen several times, giving the impression that some of the canals are apart from the main tubal canal. Study of several nearby sections reveals the actual circumstance. The same is true for the occasional specimens having a bifurcated lumen.

Without serial sections it may be impossible to distinguish between adenomyosis and serosal endometriosis, since some specimens of adenomyosis tubae may have an endometrium-like mucosal stroma. Frankl<sup>6-8</sup> and Sampson have also made this observation.

On gross examination it may be impossible to distinguish a prominent uterine cornu from a cornual nodule of adenomyosis. There exists a cornual hyperplasia or thickening of muscle without adenosis; however, for such instances only serial microscopic study can exclude the presence of the adenosis component. As much as the entire isthmus may be characterized by an unusually heavy myosalpinx. Such specimens with or without epithelial tubules are often labeled "hypertrophy" of the oviduct.

At times adhesive endosalpingitis may be so severe as to leave an apparently glandlike picture on cross section. This has been called "follicular" salpingitis by Falk.<sup>4, 5</sup> That such instances are of inflammatory origin and are not adenomyosis is immediately apparent to one who has studied sections of specimens of both diseases. Fig. 3 is a section of a specimen having an anomalous type of endosalpingeal structure; we believe it does not represent a postinflammatory residue.

For the uterus the point at which the normal structure stops and adenomyosis begins often is not evident. However, since the epithelial boundary of the oviduct is rarely violated by that epithelium, it is justifiable to designate a condition as adenomyosis when the myosalpinx is invaded by the tubal epithelium.

Often some of the tubules of adenomyosis tubae are found to be segmentally cystic. This is especially apparent where endometrium-like mucosal stroma is also present in the specimens; this may result from localized occlusions due to sanguineous desquamate. The lining of such dilated tubules has the appearance of pavement epithelium and the picture reminds one of Wolffian tubules. Von Recklinghausen, who considered "tubal angle adenomas" to be Wolffian remnants, may have studied specimens containing these segmentally cystic tubules. Within such dilated tubules the presence of an intraluminal "spur" (rudimentary plica?) probably indicates that the lesion is of Muellerian



somewhat lower. The exact frequency of their association has not been established.

The relatively high incidence of concurrence of leiomyoma uteri and tubal adenomyosis noted here and mentioned in the relevant literature is apparent rather than real. Surgically removed tissue showing both conditions is available for study because of the uterine tumor; however, cases were selected for this study solely because of the presence of adenomyosis tubae. Although the exact incidence of adenomyosis tubae among specimens of uterine leiomyomas is not at hand, it is apparent that the figure is much lower than the 30 per cent incidence of uterine leiomyomas among specimens of adenomyosis tubae which is noted here (Table VI), the height of this figure being due to the method of selection of cases for study.

Table VII shows numerically that most of the oviducts studied here which had been recognized previously as containing adenomyosis were cornual in location. Those newly discovered during the course of these examinations were particularly those wherein the enlargements were not obvious grossly, or for which the disease was diffusely distributed over the tubes and which therefore closely resembled specimens that were the site of salpingitis.

The recognition of the disease at laparotomy is greatly aided if one considers any irregularity, unusual firmness or apparent scarring of the isthmie segments of the tubes as very probably being adenomyosis. Thickening of the isthmus, if markedly at variance from the texture of the remainder of the oviduct, is quite likely to be due to adenomyosis. Tissue in situ that is the site of the disease is remarkable chiefly for its

TABLE VII. DISTRIBUTION OF ADENOMYOSIS TUBAE ALONG THE OVIDUCT

| LOCATION               | ADENOMYOSIS<br>SERIES 2* |          | REMAINDER OF 83<br>CASES* |          |
|------------------------|--------------------------|----------|---------------------------|----------|
|                        | NO.                      | PER CENT | NO.                       | PER CENT |
| 1. Entire oviduct      | 1                        | 2.6      | 4                         | 9.1      |
| 2. Ampulla only        | 0                        | 0        | 1                         | 2.3      |
| 3. Entire isthmus      | 2                        | 5.1      | 8                         | 18.2     |
| 4. Midisthmie          | 0                        | 0        | 5                         | 11.3     |
| 5. Medial isthmie only | 0                        | 0        | 8                         | 18.2     |
| 6. Cornual             | 36                       | 92.3     | 18                        | 40.9     |
| Totals                 | 39                       | 100.0    | 44                        | 100.0    |

\*These two columns are presented separately in order to show that the more diffuse type of the disease is not ordinarily recognized as such. Series 2 (see Table V), previously recognized and filed as such, is mainly constituted by the classical nodose enlargement near the tubouterine junction. Only 39 of 40 instances in Series 2 are included here because previous study of one specimen made the actual location of the disease uncertain.

The right column describes the location of the disease for 44 of the remaining 47 cases studied, 3 being omitted here for the reason given in the preceding paragraph. These specimens which had not been previously recognized as containing regions of adenomyosis were taken from the remainder of the series listed in Table V.

Where bilateral, the disease was symmetrical except for a few instances. "Cornual" (No. 6 in the table) refers to the zone of the tubouterine junction of the tube.

This table does not show the comparative frequency of the cornual and the diffuse types because the methods of their selection were not comparable. It is felt, however, that the diffuse isthmie type is more common than the classical form of the disease.

TABLE V, A. SOURCES OF THE SPECIMENS OF ADENOMYOSIS TUBAE CONSIDERED HEREIN, WITH METHODS OF THEIR SELECTION BY SERIES

|  | CASES | TUBES | CASES<br>AM.T.* |
|--|-------|-------|-----------------|
| 1. Tubal pregnancy series                  | 100   | 116   | 13              |
| 2. Control series                          | 118   | 194   | 9               |
| 3. Adenomyosis Series 1                    | 18    | 33    | 18              |
| 4. Adenomyosis Series 2                    | 40    | 71    | 40              |
| 5. Nongravid hematosalpinx series          | 45    | 71    | 7               |
| Total number of cases of adenomyosis tubae |       |       | 87              |

\*Number of cases in which there was adenomyosis tubae on one or both sides.

TABLE V, B. METHODS OF SELECTION OF THE SERIES IN TABLE V, A.

1. Consecutive series of 100 cases listed in the file of the Mayo Clinic as "tubal pregnancy," restudied for the presence of adenomyosis of the oviducts.
2. A consecutive series of cases wherein the predominant pelvic pathologic picture was not tubal. The reasons for operation among these cases were approximately the same as are given in Table VI for the 87 cases of adenomyosis tubae.
3. Specimens of adenomyosis of both tubes and uterus collected during a brief pathologic study of adenomyosis uteri, not previously recognized as also containing regions of tubal adenomyosis.
4. Previously recognized and filed as adenomyosis tubae.
5. Consecutive cases listed in the file of the Mayo Clinic as "hematosalpinx without tubal pregnancy," where the hematosalpinx was listed as an incidental finding.

TABLE VI. PRIMARY REASON FOR OPERATION\* FOR 87 CASES IN WHICH ADENOMYOSIS TUBAE WAS ALSO DISCOVERED AT PATHOLOGIC EXAMINATION

|  | CASES |
|--|-------|
| Carcinoma of the fundus uteri          | 4     |
| Menorrhagia                            | 16    |
| Sterility                              | 3     |
| Residue of pelvic inflammatory disease | 9     |
| Leiomyoma uteri                        | 26    |
| Enlargements of the ovaries            | 7     |
| Endometriosis†                         | 1     |
| Tuboovarian abscess                    | 3     |
| Tubocutaneous sinus                    | 1     |
| Prolapsus uteri                        | 2     |
| Tuberculous salpingitis                | 2     |
| Tubal pregnancy                        | 13    |
| Total                                  | 87    |

\*Pathologic diagnoses given wherever practicable.

†Total incidence indeterminate.

among 13 per cent (S.E.  $\pm$  3.4 per cent) of a series of 100 specimens of tubal pregnancy, while 9 women having adenomyosis tubae were discovered among the control series of 118 cases (7.6 per cent S.E.  $\pm$  2.4 per cent). The majority of these specimens had not been recognized previously as containing adenomyosis. Because of the method of selection of the control series, it is reasonable to suspect that 5 to 10 per cent of removed pairs of oviducts (and those of the general female population) contain adenomyosis. This must be true unless the disease is associated more frequently with leiomyoma uteri or other surgical conditions of the pelvic organs, in which event its true incidence would be

Certainly there is no agreement in the related literature concerning the patency of the tubal canal within adenomyotic segments.

On several occasions during this study, corpora amylacea have been observed within the adenomyotic tubules throughout the myosalpinx. For one specimen a collection of these bodies completely blocked the tubules, as well as the main tubal lumen at one point. The epithelium of tubules frequently disappears near such foreign bodies (pressure necrosis), leaving these bodies deep in the musculature some distance from the nearest intact tubule. For such instances, foreign body giant cells are often present so that the general aspect on microscopic examination may be that of a pseudotubercle.

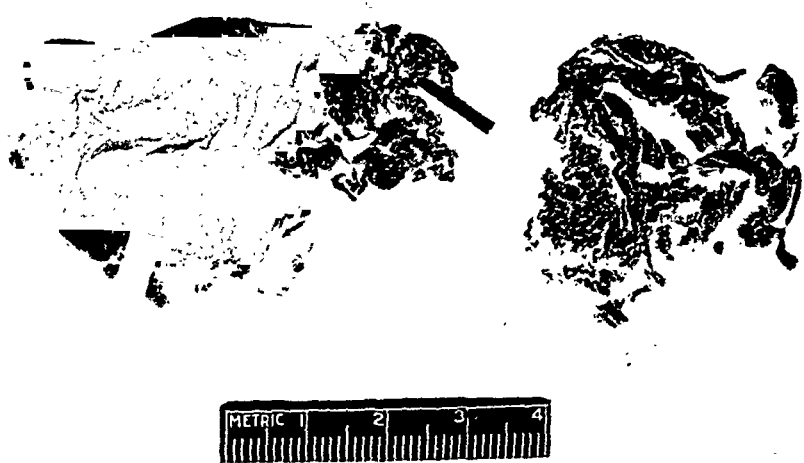


Fig. 5.—Infundibular tubal pregnancy: detached fetus and placenta at right. The nodose enlargement at the uterine end of the tube is a region of adenomyosis tubae measuring 10 by 8 by 10 mm. A section taken between this nodule and the uterus demonstrated a normal intervening segment of tube. This is a classic example of the disease sometimes called "salpingitis isthmica nodosa."

Other specimens of tubal adenomyosis for which obstruction of the lumen was known to exist are four specimens having segmental agenesia of the endosalpinx, one case having the lumina of the medial thirds of the tubes completely filled by endometrium, and six specimens in which no main lumen was discernible on study of cross section, the centers of the organs being riddled with adenomyotic canals.

In the study of the gravid oviducts which were found to contain regions of adenomyosis (13 of 100 cases of tubal pregnancy), no anatomic obstruction of the lumen could be proved or disproved without the aid of serial microscopic sections. That the adenomyosis present among these specimens may have been the cause or contributing cause of tubal nidation is suggested here not because of its presence among a greater percentage (13) than it was among the control series (7.6), since the standard errors of these two percentages show that the difference between them is not statistically significant; it is suggested, however,

resilient firmness, reminiscent of the texture of a mammary fibroadenoma. Isthmuses thickened as a result of a foregoing inflammation invariably present irregular angulations, but the resilient firmness characteristic of the usual type of adenomyosis is missing. Adenomyotic oviducts may be nodulated but are rarely markedly angled, and are quite likely to be similarly affected bilaterally.

The gross recognition of the disease in newly removed (unfixed) tissue may be difficult because of the great care required in order to accomplish a satisfactory gross examination of a cross section. Where specimens are opened axially, as is customarily done, the multiple false passages in the adenomyotic segment which usually are made by the scissors discourage its recognition. After such axial opening of the tubes, the openings of the tubules into the main tubal lumen are too small to be seen; and unless there is thickening, the disease may not be suspected. Sometimes the critical (for most instances of adenomyosis) medial tubal segment is the site of a sanguineous extravasation due to the customary application of a hemostat at this point during removal of the tube.

Fixation of the tissue, followed by examinations of cross sections cut by a sharp knife, is a requisite for the satisfactory gross identification of the less obvious types of tubal adenomyosis. Wherever present, the more abundant musculature of the involved segment is apparent, and the tubules, cut obliquely in the course through the musculature, may be seen as small gray areas, slightly different in color from the neighboring muscle.

#### PATENCY

Tubal patency in the presence of adenomyosis may be studied by the following methods: (1) extensive microscopic study of serial sections; (2) transtubal injection of fluid of fairly low viscosity using newly removed (unfixed) tissue (the simplest of the methods but one that is rarely used because the disease is infrequently recognized before fixation or axial opening); (3) postoperative tubal insufflation studies or salpingograms done "from below" after the disease has been recognized (but left untouched) at laparotomy.

For the tubal segments involved by adenomyosis studied by serial sections during these examinations, the tubal lumen has been seen to pass, compromised but uninterrupted, through most of the segments involved by adenomyosis. Obstruction was demonstrated by gross examination in only a few instances. It is reasonably certain that all of the specimens in which there was obstruction were not identified. Without serial sections for all specimens, the appraisal of the frequency and nature of such obstructions is limited. The majority of segments seem to be patent despite the high incidence of sterility (64 per cent of 39 married women having the disease in both tubes; S.E.  $\pm 7.7$  per cent).

the peritoneal cavity seems remote, although Lash has published a photomicrograph of an ovum within such a tubule. That tubal pregnancy may occur in tubal stumps containing adenomyotic tuboperitoneal fistulas (where the ovum enters the tubule from the peritoneal cavity) has been shown by Sampson. This suggests that a current toward the uterus may be present within such tubules.

Owing to the minute size of the orifices of such tubules and to the indistensibility of fixed tissues, the study of the ramifications of the tubules by roentgenologic methods after injection of radiopaque media into involved specimens is unsatisfactory for most instances. Sampson injected media into newly removed specimens and published a reproduction of a roentgenogram of such an instance. He was also able to inject a colored medium into such specimens which could be discerned in microscopic preparations. For one published specimen, this medium was shown to pass from the tubal lumen through the tubal wall and into an adherent ovarian hematoma.

The severity of inflammation in oviducts which are the sites of adenomyosis is sometimes greater than normal. Since any inflamed oviduct is likely to be removed surgically when encountered at operation, a fair answer to the question of just how conducive adenomyosis is to salpingitis is best had from study of instances of unilateral adenomyosis in which there is bilateral salpingitis. For accuracy, a considerable series would be necessary, for certainly there is great individual difference of structure of any two adenomyotic segments. Such pairs are uncommon. The impression gained from study of such instances is that the evidence of salpingitis is perceptibly more prominent on the side of the adenomyosis. The number and patency of tubules entering the main canal, the presence of endometrium-like endosalpinx, a heavier than normal myosalpinx, or of other anomalies, may all influence the course of an inflammatory process. Like an anomalous heart valve, oviducts with this anomaly may be more vulnerable to infection than normal oviducts. The relative importance of these various factors has not been assayed yet satisfactorily. Table VIII indicates the degree of leucocytic infiltration present within the adenomyotic segments in 65 of these cases.

TABLE VIII. CHARACTER AND AMOUNT OF LEUCOCYTIC INFILTRATION FOR 65 INSTANCES OF ADENOMYOSIS TUBAE

| LYMPHOCYTIC INFILTRATION | CASES |
|--------------------------|-------|
| None                     | 13    |
| Slight                   | 18    |
| Moderate                 | 19    |
| Considerable             | 5     |
| Heavy                    | 2     |
| Purulent exudate present | 8     |
| Total                    | 65    |

A gross estimation of the intensity of an instance of salpingitis is unsatisfactory here because of the thickened, nodular character of an adenomyotic segment. Excluded from this compilation are specimens showing adenomyosis from the tubal pregnancy series (13), specimens showing tuberculosis (6), plus others considered indeterminate in this respect (3); total, 87.

by the presence of the adenomyotic process in the tube at precisely the medial angle of the gravid sac for eight of these thirteen specimens, and within the wall of the sac for two other instances. For the other 3 (of the 13) the adenomyotic regions were located some distance medial to the pregnancy sac, as seen in Fig. 5.

In view of the apparent patency of the lumen for specimens of adenomyosis tubae in which there was tubal pregnancy, and because of the presence of the adenomyotic process at the medial angle of the gravid sac, suggesting a causal relation, one is led to consider other possible mechanisms by means of which adenomyosis might be responsible for tubal nidation.

Six of the 13 specimens of oviducts having both tubal pregnancy and adenomyosis also had duplication of the lumen of a length of 1 cm. or more. That this condition was not encountered among the other 74 cases of adenomyosis of the tube suggests that it may have been responsible for some of the instances of tubal nidation, although the mechanism of its action is as yet only a matter of speculation.

An unusually heavy myosalpinx is present in 89 per cent of cases of adenomyosis tubae (Table II); this may constitute the basis of an unusually high collapsing force for such segments. That spasm of oviducts not known to be the site of adenomyosis may play a part in sterility is not at all well established, but it is suggested by the decreased pressure required to initiate the transtubal insufflation of air following the administration of antispasmodic drugs (for cases in which this pressure has been found previously to be high). It has also been stated that pregnancy occasionally occurs among previously sterile women following the administration of such drugs.<sup>14</sup> The anatomy of adenomyosis tubae is such that a physiologic occlusion might be present at times owing to spasm of its heavier musculature, the latter often being five times as thick as that of the adjacent normal tube. Further knowledge concerning the relative importance of these alleged influences must come from a clinicophysiology approach, chiefly recognition at laparotomy of obstruction of the lumen by means of insufflation studies done from within the abdomen.

Adenomyosis may exert an influence on the occurrence of tubal pregnancy in other manners. The influence of endometrium-like stroma in the tube (present focally among 70 per cent of 81 of these patients, S.E.±5 per cent) will be considered elsewhere. That the tubal anomalies so frequently associated with adenomyosis of the tube might be associated with dysfunction of its transport mechanism without obstruction is another possibility, critical evidence for or against which must be obtained from both pathologic and clinical studies.

Since the points of entrance or exit of adenomyotic tubules into the main lumen and onto the serosa are so small, the possibility of a zygote gaining access to one of the tubules from within the tube or from within

mucosal stroma about the tubules may prove to be of more importance than the configuration of the tubules themselves.

The fact that many of the tubules of adenomyosis tubae penetrate the overlying serosa (Figs. 6, 7, and 8) may be quite significant, since, if the normal ostium of the tube is closed, these secondary ostia may provide vicarious passage for air to the peritoneal cavity. Such fistulas could also conduct particles of endometrium, sperm, blood, ova, or radio-paque media. However, these tubules are small, often contain sanguineous debris, and pursue a serpiginous course through the myosalpinx. These conditions militate against the leakage of contents through the accessory ostia. For instances in which a severe inflammatory process is present within the tubules, pelvic peritonitis could occur without

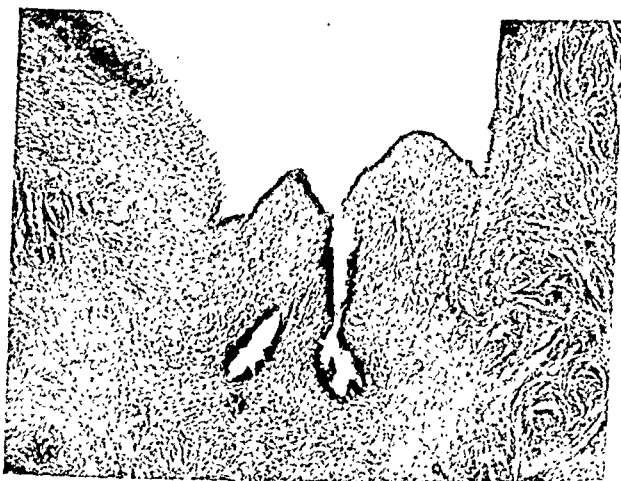


Fig. 8.—Section of medial isthmus of oviduct showing junction of the mucosa of a tubule with serosa. The transition is sharp, as it is normally at the tips of the fimbria. Note muscular anomaly. Serial sections here proved the continuity of serosa with mucosa of the main tubal lumen ( $\times 115$ ).

contaminants having traversed the lateral reaches of the tube. Furthermore, for instances in which endometrium-like mucosal stroma surrounds the tubules, and in which the internal openings of the tubules are occluded by debris or so angled as to be obstructed, small amounts of blood derived from the uterus, the isthmus of the tube, or the tubule might be found in the cul-de-sac of Douglas without having traversed the natural ostium of the tube.

Since a detailed description of such conditions can be had only at laparotomy, the acquisition of further information relative to the importance (or lack of it) of adenomyosis tubae will be greatly aided by its wider recognition at the time of operation and by accurate descriptions of operative findings by many observers.

Phillips, quoted by Dougal, has said that cornual "endometriosis" is a rare but important cause of unilateral dysmenorrhea. There is some reason to believe that the disease to which he referred may have

The abundance of muscle noted in adenomyotic segments of tube, and the fact that the numerous epithelial processes (of considerable total length) may discharge their contents into a relatively short segment



Fig. 6.—The lower half of the figure is the periphery of the oviduct while the upper portion is a flap of serosa capping a tubule which has penetrated the myosalpinx. Serial sections showed this tubule to be in continuity with the tubules below, which in turn are in continuity with the main tubal lumen at the isthmus ( $\times 90$ ).

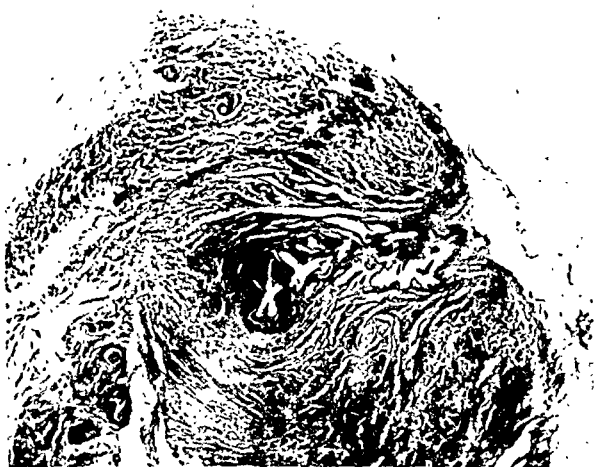


Fig. 7.—Cross section of the medial portion of an oviduct containing an adenomyotic tuboperitoneal fistula. The actual seromucosal junction is not seen in this section; it was located a few sections distant. No serosal endometriosis present; no endometrium-like endosalpinx present. The general aspect of this muscular anomaly is that of a failure of closure of two lips ( $\times 18$ ).

tube, are factors which may interfere with the emptying of the organ. Blood or tubal contents discharged into such short segments conceivably could diminish the emptying capacity of the tube and protract an inflammatory process. As a contributing cause of salpingitis, the type of



If the residue of inflammation is evident about the tubal fimbriae, it is probable that the isthmus of that tube is open; in this event the problem is not concerned with adenomyosis, but rather with the advisability of a plastic operation on the tubal ampulla or the Estes operation. The low incidence of pregnancy subsequent to procedures of this type is well known. Here is a fertile field for study.

At present it is sufficient to state that the only indication for a reconstructive operation for adenomyosis tubae is in the event of a patient who wants children, who already has experienced a reasonably long period of sterility, and on whom tests of patency done from within the abdomen have demonstrated isthmic obstruction on both sides. If the medial segments of the tubes only are involved, a reasonable course consists of segmental resections with reimplantations, followed by frequent postoperative insufflations "from below." Where the entirety of each tube is involved by adenomyosis, or where both tubes are hopelessly obstructed, the Estes operation is the only procedure offering any hope at all for pregnancy.

There is no reason to believe that adenomyosis of the tube undergoes malignant degeneration in other than extremely rare instances.

As has been pointed out by others, the propensity of adenomyotic tubules to grow from a tubal stump and to penetrate the tubal wall suggests again the need for excision of the intramural portion of the tube when salpingectomy without hysterectomy is undertaken.

#### SUMMARY

The classic form of adenomyosis of the tube is characterized by the presence in a firm and thickened segment of medial tubal isthmus of multiple, small, tubular diverticuli of the endosalpinx which pursue a serpiginous course through the tubal wall. The disease is bilateral for about 85 per cent of the cases studied herein.

The diffuse form of adenomyosis tubae, probably the more common type, is not identified as often as is the localized form, which is characterized by a nodose isthmus. This is true at operation because of the tendency of most surgeons to consider most types of tubal disease to be postinflammatory states (which this condition closely resembles). It is also true at gross pathologic examination because the customary method of such examination consists of axial opening of the organ by scissors. This maneuver leaves the disease difficult to discern. In situ, the presence of a resilient, firm segment of isthmus, with or without enlargement of that portion (where the ampulla is within normal limits) usually suffices to identify the disease. At pathologic examination, cross sectional study after fixation is the method best suited for identification of the less obvious type.

Evidence is submitted which suggests that the disease may not be a result of inflammation. Not the least of this evidence is the rather

been adenomyosis tubae. Among the records of the present series of 87 women who had adenomyosis tubae, no history of unilateral dysmenorrhea has been encountered; in fact, these records are singularly free of mention of this symptom. No significant item has been found which would permit preoperative recognition of the usual form of the disease. Of course, prolonged sterility without discernible cause strongly suggests it, and isthmic obstruction as discerned in salpingograms likewise suggests adenomyosis tubae.

#### SURGICAL DISPOSITION

What shall a surgeon do on encountering the disease at operation? If the uterus is to be removed for another reason, the question of salpingectomy resolves itself easily. For women past the childbearing age, having otherwise normal genitals, no evidence is provided by this study which might suggest that removal of the tubes is justified for the simple fact that adenomyosis is present. Where pain is the primary reason for laparotomy, removal of adenomyotic oviducts can hardly be expected to be of aid in the light of the infrequency of history of dysmenorrhea among the women whose oviducts have been studied here. The question of whether or not adenomyosis of the uterus causes painful menstruation is outside the scope of this study.

If the operation is undertaken on a woman who desires children, the problem is not so simple. It is imperative that proper distinction be made between chronic salpingitis and adenomyosis, since some apparently hopeless oviducts which are the site of adenomyosis are patent. After the injection of procaine into the regions of the hypogastric ganglia and along the uterine and ovarian arteries (intended to minimize isthmospasm), tubal patency may be tested from within the abdomen by means of a syringe and needle. If one or both tubes are patent (where the disease is encountered incidentally), the tubes are best left untouched, for although the incidence of sterility of married women of this series of cases (where both tubes were involved) was 64 per cent, that following tubal resection with reimplantation or the Estes operation is considerably higher. If these operations were more generally successful, indications for their performance might be more liberal. However, where there has been sterility of long standing, reimplantation undoubtedly offers more hope of temporary patency than does leaving the lesion *in situ*.

There is some evidence to indicate that women who have adenomyosis and whose oviducts are patent on one or both sides are more likely to experience tubal pregnancy than are women who have no tubal adenomyosis. Whether this risk is accepted may reasonably depend on the attitude of the patient as determined before operation. When the isthmus of one tube is obstructed and when its mate is open, it is likely that tubal pregnancy will be less probable if the adenomyotic tube is excised.

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## DOES THE ANTENATAL USE OF VITAMIN K PREVENT HEMORRHAGE IN THE NEWBORN INFANT?\*

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FOR the past three years there has been widespread interest in the study of vitamin K as an agent for the prevention and treatment of hemorrhage in the newborn infant. There have been numerous reports<sup>1</sup> indicating that in infants whose mothers receive vitamin K a few hours before delivery and in infants who receive the substance immediately after birth, the blood prothrombin level is raised and the neonatal drop in prothrombin is greatly reduced or entirely absent.

In attempts to apply these findings clinically, there have been two reports<sup>2, 3</sup> in which vitamin K has been given to fairly large groups of women during labor. In each instance, the authors reported a definite reduction of neonatal hemorrhage in the infants whose mothers had received vitamin K as compared with those whose mothers were not so treated.

On the basis of these reports, we were stimulated to undertake a controlled study of the value of vitamin K given during labor in preventing hemorrhage in the newborn infants of a group of indigent mothers.

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high incidence of other tubal anomalies among specimens of adenomyosis tubae.

For 65 to 75 per cent of 81 cases, a mucosal stroma resembling endometrium rather than endosalpinx has been encountered focally beneath the tubal type of tubule lining. This stroma will be described separately.

For 39 married women who had the disease on both oviducts, the incidence of sterility was found to be 64 per cent ( $\pm 8$  per cent\*). The mechanism of this feature of the disease is not well understood; several possible mechanisms have been suggested.

Adenomyosis tubae does not cause dysmenorrhea, although adenomyosis of the uterus is widely held to do so. The frequency of association of adenomyosis tubae and adenomyosis uteri has not been determined.

The tendency of the tubules of adenomyosis tubae is to penetrate the myosalpinx and overlying serosa with formation of multiple tuboperitoneal fistulas. These channels, although small, may provide vicarious passage for sperm, ova, blood, bacteria, opaque media used for diagnosis, or endometrial particles between the tubal lumen and the peritoneal cavity.

Adenomyosis tubae was discovered among 13 per cent ( $\pm 3.4$  per cent\*) of specimens of tubal pregnancy, and among 7.6 per cent ( $\pm 2.4$  per cent\*) of a control series. Where these two conditions are associated in one specimen the adenomyotic process often involves the tube at precisely the medial angle of the pregnancy sac.

Adenomyosis of the tube is suggested clinically by a long period of sterility without apparent cause, and by isthmie obstruction as seen by salpingogram.

The aim of this presentation is the stimulation of widespread recognition of the disease so that problems concerning the patency of tubes in which it is present, as well as many other problems, may be decided. It is probably present among 5 to 10 per cent of the general female population. Further information concerning it awaits large-scale recognition, with clinical, pathologic and physiologic study of its relation to serosal endometriosis, endometrium-like endosalpinx, sterility and many other problems.

It is likely that little will be accomplished surgically for the condition until there is improvement in the technique of tubal resection and reimplantation.

It is felt that the disease may be more significant than is generally recognized.

A discussion of its surgical disposition is included.

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\*Standard error.

showed a cord blood prothrombin level which was approximately 20 per cent above the cord levels of untreated patients.

In another small unselected group of infants from each series, blood prothrombin levels were done daily for the first week of life. Our findings coincided entirely with those previously reported;<sup>1</sup> that is, in normal untreated infants there is a marked drop in blood prothrombin level for the first three or four days, followed by a rise to normal. In infants whose mothers receive vitamin K four hours or more before delivery, this drop is much less pronounced.

The specific treatment of infants showing clinical evidence of gross hemorrhage consisted of the administration of oral or intramuscular vitamin K and of intramuscular or intravenous injections of blood as outlined in Tables IV and V.

### RESULTS

The incidence of hemorrhage has been correlated with the period of hospitalization before delivery, the type of delivery, and the maturity of the infant as judged by the weight. Abnormal bleeding occurred in 22, or 1.4 per cent, of 1,594 infants whose mothers received no vitamin K and in 20, or 1.7 per cent, of 1,151 infants whose mothers received vitamin K on admission.

It is of interest to note that the incidence of hemorrhage is essentially the same as that reported in the control series of Hellman, Shettles, and Eastman,<sup>2</sup> and of Beck, Taylor, and Colburn.<sup>3</sup> If only the types of hemorrhage that we have included are considered from the totals reported by Sanford and his co-workers,<sup>5</sup> the incidence of abnormal bleeding in their total series is comparable to ours.

Table I shows the incidence of hemorrhage in infants with relation to the period of hospitalization and the administration of vitamin K to the mothers. There was very little difference in the percentage incidence of hemorrhage in those infants whose mothers received vitamin K a short while or a long while before delivery. Nine, or 1.8 per cent, of 509

TABLE I. INCIDENCE OF HEMORRHAGE IN INFANTS WITH RELATION TO THE PERIOD OF HOSPITALIZATION AND THE ADMINISTRATION OF VITAMIN K TO MOTHERS DURING LABOR

| HOURS IN HOSPITAL BEFORE DELIVERY | MOTHERS RECEIVED NO VITAMIN K |                         | MOTHERS RECEIVED VITAMIN K ON ADMISSION |                         |
|-----------------------------------|-------------------------------|-------------------------|---|-------------------------|
|                                   | NO. OF INFANTS                | INFANTS WITH HEMORRHAGE | NO. OF INFANTS                          | INFANTS WITH HEMORRHAGE |
| Four or less                      | 841                           | 7 or 0.8%               | 509                                     | 9 or 1.8%               |
| Over four through twenty-four     | 578                           | 5 or 0.9%               | 526                                     | 8 or 1.5%               |
| Over twenty-four                  | 175                           | 10 or 5.7%              | 116                                     | 3 or 2.6%               |
| Total                             | 1,594                         | 22 or 1.4%              | 1,151                                   | 20 or 1.7%              |

infants born within four hours after the administration of vitamin K showed hemorrhage. There were 8 patients, or 1.5 per cent, with hemorrhage in 526 infants born between four and twenty-four hours after the mothers received the drug. In the treated series, among 116 infants who were born over twenty-four hours after admission, there were 3 infants, or 2.6 per cent, who showed hemorrhage. In two of these infants, the hemorrhage was definitely due to traumatic delivery (see Table V).

## PROCEDURE

Women admitted to the obstetric department of Gallinger Municipal Hospital are assigned alternately to the services of George Washington and Georgetown University Medical Schools. All patients are under the immediate supervision of one full-time obstetrician, one full-time pediatrician, and the same house staffs. With regard to the types of delivery, analgesia, and general obstetric and pediatric care, there is no appreciable difference between the two services.

From Oct. 7, 1940, to Jan. 17, 1942, mothers admitted to the George Washington service were given a single dose of 5 mg. of vitamin K\* (2 methyl 1, 4 naphthoquinone) by mouth immediately after admission to the obstetric ward. Mothers admitted to the Georgetown service were used as controls. During the fifteen months of the study, approximately 140 women admitted to the George Washington service failed to receive vitamin K through an oversight of the attending physician or nurse. Since there was no intentional selection of these cases, they were added to the control group. There were 163 infants born to mothers whose records failed to indicate whether or not they had received vitamin K as ordered. This latter group was excluded from the series. Also excluded from the control and treated groups were: (1) All fetuses weighing less than 1,000 Gm. at birth; (2) 49 stillborn infants who showed no sign of life at the time the mothers were admitted to the hospital; and (3) 34 live-born infants who were delivered so soon after admission that no therapy could have been given to the mothers. All other infants born in the hospital are included in the series. The treated series comprises 1,151 infants whose mothers received vitamin K fifteen minutes to several days before delivery. The control series consists of 1,594 infants whose mothers received no vitamin K.

The infants of the treated mothers and the infants of those who served as controls were observed during their period of hospitalization for evidences of hemorrhage. Only grossly abnormal hemorrhage was considered; that is, definite melena neonatorum, hematemesis, continued bleeding from the cord after adequate ligature, gross subcutaneous or cutaneous hemorrhage, definite intracranial hemorrhage, or hemorrhage into the adrenal glands. These serious types of hemorrhage were recorded from clinical and post-mortem findings. Milder forms of hemorrhage such as vaginal bleeding, subconjunctival hemorrhage, cephalohematoma, or the vomiting of a small amount of brownish material shortly after birth were not included unless they were accompanied by other, more severe hemorrhagic manifestations.

In order to test the potency of the preparation used, microprothrombin tests were done on both mothers and infants by the method of Abramson and Weinstein.<sup>4</sup> In a group of unselected patients, the mother's blood prothrombin level was determined on admission. The determination was repeated on the mother's blood and on the cord blood at the time of delivery. In 30 untreated patients, the cord blood prothrombin level was approximately 15 per cent lower than the maternal blood prothrombin at the time of delivery. In 35 mothers who received 5 mg. of vitamin K by mouth, similar prothrombin determinations were made. The infants of mothers, treated at least four hours before delivery,

\*Supplied by the Department of Medical Research, Winthrop Chemical Co.

TABLE IV. ANALYSIS OF THE 22 INFANTS WHO SHOWED HEMORRHAGE FROM THE GROUP OF 1,594 MOTHERS WHO RECEIVED NO VITAMIN K

| NO. | TYPE OF DELIVERY | WEIGHT (GM.) | TIME IN HOSPITAL BEFORE DELIVERY | TYPE AND TIME OF HEMORRHAGE     | RESULT         | REMARKS AND AUTOPSY FINDINGS  |
|-----|------------------|--------------|----------------------------------|---------------------------------|----------------|---|
| 1   | Low forceps      | 4,025        | 5½ hr.                           | Subcutaneous on the third day   | Recovered      | Prothrombin less than 10%. Vit. K 5 mg. orally. Prothrombin increased to 100 per cent. R.B.C. 2,700,000; transfusion                    |
| 2   | Spontaneous      | 1,985        | 2½ hr.                           | Generalized cutaneous third day | Died 14 days   | Prothrombin less than 20%. Vit. K 6 mg. Transfusion. Bleeding stopped. Died 11 days later of infection. Had syphilis. No autopsy        |
| 3   | Cesarean section | 3,630        | 5 days                           | Gastric on second day           | Recovered      | On 10/13/41, prothrombin 8%. Vit. K 1.5 mg. orally. On 10/14/41, prothrombin 5%, Vit. K 1.5 mg. orally. 10/15/41, prothrombin 50%       |
| 4   | Spontaneous      | 4,480        | 4 days                           | Gastric on first day            | Recovered      | Prothrombin 30%. Vit. K 2 mg. I.M. Four hours later prothrombin 44%   |
| 5   | Breech           | 2,125        | 2½ hr.                           | Gastric on seventh day          | Died 9 days    | 11/16/41, prothrombin 33%. Vit. K 6 mg. I.M. Prothrombin 80%. Bleeding stopped. Died 11/17/41. Clinical diagnosis pneumonia. No autopsy |
| 6   | Spontaneous      | 3,315        | 1¼ hr.                           | Gastric on third day            | Recovered      | Prothrombin not done. Vit. K 2 mg. I.M.   |
| 7   | Spontaneous      | 3,175        | 11 hr.                           | Cord on first day               | Recovered      | Prothrombin not done. 20 c.c. whole blood intramuscularly   |
| 8   | Cesarean section | 1,560        | 9 days                           | Adrenal                         | Died at 6 days | 6/16/41, bullous impetigo. Died on 6/17/41 with massive bilateral adrenal hemorrhage  |

The greatest prophylactic value from vitamin K given orally is said to be obtained in infants born between four and twenty-four hours after the mothers have received the preparation. In our study of infants born in this time interval after admission to the hospital, 8, or 1.5 per cent, of the infants of treated mothers compared with 5, or 0.9 per cent, of the control infants, showed evidence of hemorrhage. This comparison indicates no reduction in the incidence of hemorrhage in infants born from four to twenty-four hours after the antenatal administration of vitamin K.

With reference to the infants born over twenty-four hours after admission, there is an apparent, but not statistically significant difference in the percentage of hemorrhage occurring in the treated and untreated infants. The difference can be accounted for, in a large measure, by the greater incidence of definitely traumatic deliveries in the untreated series (see Tables IV and V).

With regard to the administration of vitamin K after admission to the hospital, an analysis of all our data brings out a point of extreme importance from the public health and administrative standpoint. We have recorded information on 2,942 infants, a part of whom have not been used as controls or treated cases for reasons stated above. Of this group of 2,942 infants, 922, or 31.3 per cent, were born within two hours after admission and 1,479, or 50.1 per cent, were born within four hours after admission to the hospital. It is quite certain that oral vitamin K will be ineffective in raising the infant's blood prothrombin level when given to the mothers within two hours of delivery, and it is

TABLE II. INCIDENCE OF HEMORRHAGE IN PREMATURE AND FULL-TERM INFANTS WITH RELATION TO THE ADMINISTRATION OF VITAMIN K TO MOTHERS DURING LABOR

| WEIGHT OF INFANTS                         | MOTHERS RECEIVED NO<br>VITAMIN K |                            | MOTHERS RECEIVED<br>VITAMIN K ON ADMISSION |                            |
|---|----------------------------------|----------------------------|--|----------------------------|
|   | NO. OF<br>INFANTS                | INFANTS WITH<br>HEMORRHAGE | NO. OF<br>INFANTS                          | INFANTS WITH<br>HEMORRHAGE |
| Premature infants<br>(1,000 to 2,499 Gm.) | 210                              | 7 or 3.3%                  | 132  | 6 or 4.5%                  |
| Full-term infants<br>(2,500 Gm. or over)  | 1,384                            | 15 or 1.1%                 | 1,019                                      | 14 or 1.4%                 |
| Total                                     | 1,594                            | 22 or 1.4%                 | 1,151                                      | 20 or 1.7%                 |

TABLE III. INCIDENCE OF HEMORRHAGE IN INFANTS WITH RELATION TO TYPE OF DELIVERY AND THE ADMINISTRATION OF VITAMIN K TO MOTHERS DURING LABOR

| TYPE OF DELIVERY | MOTHERS RECEIVED NO<br>VITAMIN K |                            | MOTHERS RECEIVED<br>VITAMIN K ON ADMISSION |                            |
|------------------|----------------------------------|----------------------------|--|----------------------------|
|                  | NO. OF<br>INFANTS                | INFANTS WITH<br>HEMORRHAGE | NO. OF<br>INFANTS                          | INFANTS WITH<br>HEMORRHAGE |
| Spontaneous      | 1,307                            | 7 or 0.5%                  | 923  | 13 or 1.4%                 |
| Forceps          | 180                              | 7 or 3.9%                  | 165  | 4 or 2.4%                  |
| Breech           | 79                               | 5 or 6.3%                  | 49   | 3 or 6.0%                  |
| Cesarean section | 28                               | 3 or 10.7%                 | 14   | 0                          |
| Total            | 1,594                            | 22 or 1.4%                 | 1,151                                      | 20 or 1.7%                 |



TABLE V. ANALYSIS OF THE 20 INFANTS WHO SHOWED HEMORRHAGE FROM THE GROUP OF 1,151 MOTHERS WHO RECEIVED VITAMIN K ON ADMISSION

| NO. | TYPE OF DELIVERY | WEIGHT (GM.) | TIME IN HOSPITAL BEFORE DELIVERY | TYPES AND TIME OF HEMORRHAGE        | RESULT          | REMARKS AND AUTOPSY FINDINGS   |
|-----|------------------|--------------|----------------------------------|-------------------------------------|-----------------|--|
| 1   | Spontaneous      | 1,445        | 32¾ hr.                          | Mouth, nose and anus.<br>Second day | Died at 2 days  | Prothrombin not done; slight bloody vomitus at 6 A.M.; Vit. K 2 mg. I.M. at 8:30 A.M. and at 9 A.M. Bleeding more profuse; died at 10:30 A.M. Hemorrhage into lungs and gastrointestinal tract |
| 2   | Spontaneous      | 3,215        | 17 hr.                           | Intestinal on third day             | Recovered       | Prothrombin not done. Vit. K 2 mg. I.M. and 6 mg. orally   |
| 3   | Spontaneous      | 2,765        | 2¾ hr.                           | Intestinal on fifth day             | Recovered       | Prothrombin 100%. R.B.C. 1,000,000. Two blood transfusions   |
| 4   | Spontaneous      | 3,680        | 2½ hr.                           | Intestinal on fifth day             | Recovered       | Prothrombin not done. Vit. K 4 mg. I.M.  |
| 5   | Low forceps      | 3,030        | 19½ hr.                          | Gastric on second day               | Recovered       | Vit. K 2 mg. I.M. and 2.5 mg. orally; bleeding continued for 2½ hours  |
| 6   | Spontaneous      | 3,275        | 2¼ hr.                           | Gastric on first day                | Recovered       | Prothrombin 27%. Vit. K 2 mg. I.M. Two hr. later prothrombin was 95%   |
| 7   | Spontaneous      | 3,780        | 1¾ hr.                           | Cord on first day                   | Recovered       | Prothrombin 50%. Vit. K 3 mg. orally. Prothrombin next day was 64%   |
| 8   | Breech           | 1,369        | ½ hr.                            | Adrenal at birth                    | Died at 5 hours | Cerebral edema and adrenal hemorrhage  |

|    |                         |       |         |                                     |                  |  |
|----|-------------------------|-------|---------|-------------------------------------|------------------|--|
| 9  | Breech                  | 1,415 | 3¾ hr.  | Petechial at birth                  | Died 1 hr.       | Petechiae in lungs, thymus, and heart  |
| 10 | Midforceps              | 3,005 | 22½ hr. | Petechiae and intracranial at birth | Died intrapartum | Petechiae in heart. Cerebral hemorrhage. No rupture of vessels seen  |
| 11 | Spontaneous             | 2,720 | 7 days  | Intracranial at birth               | Died intrapartum | Cerebral Hemorrhage. No rupture of vessels seen  |
| 12 | Breech                  | 1,560 | 1½ hr.  | Intracranial                        | Died 7 days      | Diarrhea on fourth day. Prothrombin not done. Massive intracranial and intraventricular hemorrhage. No rupture of vessels seen |
| 13 | Cesarean section        | 2,130 | 20 days | Clinical intracranial at birth      | Died 2 days      | Prothrombin not done. Vit. K 2 mg. I.M. and 2 mg. orally. Transfusion. No post mortem  |
| 14 | Low forceps             | 4,310 | 4 days  | Intracranial at birth               | Died 36 hr.      | Ruptured cerebral vessels.   |
| 15 | Version and ex-traction | 5,370 | 3 days  | Intracranial at birth               | Died 19 hr.      | Ruptured cerebral vessels. Adrenal hemorrhage  |
| 16 | Midforceps              | 4,055 | 3 days  | Intracranial                        | Died intrapartum | Ruptured cerebral vessels  |
| 17 | Spontaneous             | 3,495 | 2 days  | Intracranial                        | Died intrapartum | Ruptured cerebral vessels  |
| 18 | Midforceps              | 4,990 | 2 days  | Intracranial                        | Died intrapartum | Ruptured cerebral vessels  |
| 19 | Midforceps              | 4,280 | 16¾ hr. | Intracranial at birth               | Died 1 day       | Ruptured cerebral vessels and hydrocephalus  |
| 20 | Spontaneous             | 1,090 | 12 hr.  | Intracranial                        | Died 6 hr.       | Ruptured cerebral vessels  |
| 21 | Midforceps              | 3,035 | 3 hr.   | Intracranial                        | Died intrapartum | Ruptured cerebral vessels  |
| 22 | Version and ex-traction | 3,630 | 1½ hr.  | Intracranial at birth               | Died first hour  | Ruptured cerebral vessels  |

doubtful that it will have much effect if given within less than four hours of delivery. At least one-third and probably one-half of our patients entered the hospital too late for the drug, administered immediately by mouth, to exert any influence. It is probable that this experience will be repeated in other large municipal institutions.

The relationship of the administration of vitamin K to the occurrence of hemorrhage in premature and mature infants is shown in Table II. In the control group, there were 210 premature infants with 3.3 per cent hemorrhage and 1,384 full-term infants showing abnormal hemorrhage in 1.1 per cent. The vitamin K treated series contained 132 premature infants with 4.5 per cent hemorrhage and 1,019 full-term infants with 1.4 per cent hemorrhage. While both groups showed severe hemorrhage about three times as frequently in premature as compared with full-term infants, there was no significant statistical difference in the percentage of hemorrhage occurring in treated and untreated full-term and in treated and untreated premature infants.

Table III shows no significant reduction in the incidence of hemorrhage in infants whose mothers received vitamin K with relation to the type of delivery. Hemorrhage was less in the control group of infants born by spontaneous delivery; the control infants born by forceps delivery and by cesarean section showed a slightly higher percentage of hemorrhage than in the treated series. The differences are not great enough to be of statistical significance.

A detailed analysis of the infants with hemorrhage in the two groups of patients is given in Tables IV and V. There was a striking similarity of the hemorrhagic manifestations in the two groups of infants with the single exception that rupture of the cerebral vessels was found as a cause of intracranial hemorrhage much more frequently in the control than in the treated group. In the treated group there were 12 and in the control group 13 infants with intracranial hemorrhage. In the control series, ruptured cerebral vessels were found to be the cause of hemorrhage in 9 infants; in the treated series, ruptured vessels were found in only 4 of the 12 infants with cerebral hemorrhage. Intracranial hemorrhage, without definite evidence of trauma, was found more frequently in the treated than in the untreated infants. In the two groups, there was no appreciable difference in the number of infants showing gastrointestinal, cutaneous, umbilical cord, or adrenal hemorrhage.

Among 1,594 infants whose mothers received no vitamin K, there were 78, or 4.9 per cent, fetal deaths. There were 47 deaths, or a fetal mortality of 4.1 per cent, among the 1,151 infants of treated mothers. Included in both groups are all infants showing evidence of life on admission, but dying during labor, and all neonatal deaths occurring within two weeks after birth. Since there were 31 autopsies in 47 fetal deaths (66 per cent) in the treated series and 55 autopsies in 78 fetal deaths (70.5 per cent) in the control series, the post-mortem findings in the two groups should be comparable. A complete list of the recorded causes of fetal deaths in both groups of patients is given in Table VI. Hemorrhage, not definitely due to trauma, was associated with approximately 10 per cent of the fetal deaths. Traumatic hemorrhage, anoxia, prematurity, congenital abnormalities, and infections continued to account for about 85 per cent of our fetal mortality.

|    |                        |       |         |                                     |                  |  |
|----|------------------------|-------|---------|-------------------------------------|------------------|--|
| 9  | Spontaneous            | 3,445 | 8½ hr.  | Clinical intracranial.<br>First day | Recovered        | Prothrombin 56%; whole blood 20 c.c. I.M.  |
| 10 | Spontaneous            | 2,720 | 21¾ hr. | Intracranial                        | Died intrapartum | Cerebral hemorrhage with no rupture of vessels found   |
| 11 | Spontaneous            | 2,185 | 17 hr.  | Intracranial                        | Died at 12 days  | On eleventh day developed diarrhea and pneumonia. Prothrombin not done. Cerebral hemorrhage with no rupture of vessels found. Bronchopneumonia |
| 12 | Spontaneous            | 2,360 | 9¾ hr.  | Intracranial                        | Died at 13 hr.   | Prothrombin 21%. Vit. K 2 mg. I.M. Mild cerebral hemorrhage with no rupture of vessels   |
| 13 | Low forceps            | 3,590 | 7½ hr.  | Intracranial                        | Died at 5 days   | Cyanotic from birth. Prothrombin 67%. Vit. K 4 mg. I.M. Cerebral hemorrhage with no rupture of vessels found. Aspiration pneumonia             |
| 14 | Spontaneous            | 1,675 | 4½ hr.  | Intracranial at birth               | Died at 12 hr.   | Subtentorial hemorrhage with no rupture of vessels found   |
| 15 | Breech                 | 3,145 | 2½ hr.  | Intracranial at birth               | Died at 6 hr.    | Cerebral hemorrhage with no rupture of vessels found   |
| 16 | Spontaneous            | 4,025 | 2 hr.   | Intracranial                        | Died at 6 days   | Died suddenly on sixth day. Bronchopneumonia and cerebral hemorrhage with no rupture of vessels found  |
| 17 | Midforceps             | 3,290 | 6 days  | Intracranial at birth               | Died at 10 hr.   | Prothrombin 14%. Vit. K 2 mg. I.M. Ruptured cerebral vessels and petechiae of pleura   |
| 18 | Version and extraction | 3,190 | 31 hr.  | Intracranial at birth               | Died intrapartum | Ruptured cerebral vessels  |
| 19 | Midforceps             | 3,460 | 1 hr.   | Intracranial and adrenal            | Died intrapartum | Ruptured cerebral vessels and adrenal hemorrhage   |
| 20 | Spontaneous            | 1,715 | ¾ hr.   | Intracranial at birth               | Died at 15 hr.   | Ruptured cerebral vessels  |

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## PREGNANEDIOL DETERMINATIONS IN GYNECOLOGY AND OBSTETRICS\*

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**M**ANY disturbances of gynecologic and obstetric functions have been related by fact or by theory to altered levels of progestin elaboration. Since objective and accurate definition of these levels still remains a diagnostic problem, much therapy employing progestin has been founded upon presumed rather than upon established functional pathology.

Venning's gravimetric method for determining urinary pregnanediol (a metabolic product of progestin),<sup>1</sup> described in 1937, aroused the hope that it would permit practical quantitations of progestin levels in clinical practice. During the past four years correlational studies designed to evaluate this method have been pursued by our group. In all 7,114 twenty-four-hour specimens of urine of 233 women have been quantified for pregnanediol. Conclusions regarding practical application of the method to gynecologic and obstetric practice are reported in this communication.

\*Read by invitation by E. C. Hamblen at a meeting of the Washington Gynecologic Society, March 28, 1942.

None of the mothers showed any intolerance to vitamin K. Vitamin K seemed to exert no influence on the incidence of puerperal morbidity, thrombophlebitis, or maternal mortality.

TABLE VI. AN ANALYSIS OF FETAL DEATHS OCCURRING IN THE CONTROL AND IN THE VITAMIN K TREATED SERIES OF INFANTS

| 1,594 INFANTS WHOSE MOTHERS RECEIVED<br>NO VITAMIN K |            | 1,151 INFANTS WHOSE MOTHERS RECEIVED<br>VITAMIN K ON ADMISSION |            |
|--|------------|--|------------|
| Total number infants died                            | 78 (4.9%)  | Total number infants died                                      | 47 (4.1%)  |
| Premature infants died                               | 51 (65.4%) | Premature infants died   | 32 (68.1%) |
| Full-term infants died                               | 27 (34.6%) | Full-term infants died   | 15 (31.9%) |
| Stillbirths  | 27 (34.6%) | Stillbirths  | 8 (17%)    |
| Intracranial hemorrhage<br>(Traumatic, 4)            | 6          | Intracranial hemorrhage<br>(Traumatic, 2)                      | 3          |
| Anoxia   | 11         | Anoxia   | 3          |
| Craniotomy   | 2          | Craniotomy   | 1          |
| Congenital abnormality                               | 1          | Toxemia (eclampsia)  | 1          |
| Intrauterine infection                               | 3          |  |            |
| Cause unknown  | 4          |  |            |
| Live births  | 51 (65.4%) | Live births  | 39 (83%)   |
| Intracranial hemorrhage<br>(Traumatic, 5)            | 6          | Intracranial hemorrhage<br>(Traumatic, 2)                      | 5          |
| Infection  | 9          | Infection<br>(Intracranial hem., 3)                            | 12         |
| Gastrointestinal hem.                                | 1          | Gastrointestinal hem.  | 1          |
| Congenital abnormalities<br>(Intracranial hem., 1)   | 5          | Cerebral edema   | 2          |
| Anoxia   | 6          | Anoxia   | 3          |
| Prematurity (no other cause<br>found)                | 23         | Prematurity (no other<br>cause found)                          | 15         |
| Cause unknown  | 1          | Cause unknown  | 1          |

#### SUMMARY AND CONCLUSIONS

We have made a careful clinical analysis of gross hemorrhage occurring in the infants of mothers admitted to a municipal hospital. These mothers represent the lowest income group of a metropolitan area. It is reasonable to assume that dietary deficiencies and obstetric complications should be maximal in this group of patients. If these factors contribute materially to the occurrence of hemorrhage in the newborn, any procedure directed toward the reduction of neonatal hemorrhage should manifest its greatest benefits in patients of the lowest economic level such as we have studied.

A single dose of 5 mg. of vitamin K was given by mouth on admission to the mothers of 1,151 infants; the infants of 1,594 mothers who received no vitamin K served as controls. There was no appreciable ill effect of the vitamin on the mothers. As it was done in this study, the administration of vitamin K to mothers *had no evident effect in reducing the incidence of neonatal hemorrhage*. The vitamin K used was effective in raising the blood prothrombin levels of both the mothers and infants. If an elevated blood prothrombin level is a significant factor in preventing neonatal hemorrhage, we are unable to explain the results of our clinical survey. Additional clinical and laboratory studies involving large groups of patients should clarify this question.

the degree of responsiveness and by the ability of effective utilization which characterize the endometrium. A simple system for the grading of progestational responses which was designed and is used by us follows:

- M-, minimal and irregular (patchy) progestational response
- M, moderate and irregular (patchy) progestational response
- M+, marked but irregular (patchy) progestational response
- P-, minimal (immature) but regular progestational response
- P, normal progestational response
- P+, marked (decidualike) progestational response

5. *Pregnanediol Method*.—Of the 4 types of studies discussed to this point, only the biopsy method has permitted practical application. For the most part, the endometrial data secured permit only qualitative information regarding ovarian function during nonpregnant cycles and are not available during the gestational cycle.

When Venning provided a gravimetric method for the estimation of the sodium pregnanediol glucuronide content of urine and when she and her associates<sup>1</sup> submitted evidence that this steroid-complex might represent a major metabolic product of progesterin, the hope was aroused that this technique would permit an accurate, practical and quantitative means of estimating clinically progesterin levels both in the nonpregnant and pregnant states.

Other methods for the estimation of urinary pregnanediol have been described by Veitsch and associates<sup>6</sup> and by Bachman and his group.<sup>7</sup> Our work<sup>8</sup> has been confined strictly to the employment of Venning's technique. Our faithful adherence to this technique has been favored by having a research associate during a part of our studies who was common to both groups (C. J. P.).

#### METHODS

The Venning technique has been described in detail by its author. Certain generalizations regarding it are judged to be pertinent to the present discussion.

The routine requires repeated and consecutive examinations of twenty-four-hour specimens of urine during the nonbleeding phase of the ovarian cycle to be sampled and continuous examinations of all twenty-four-hour specimens during the gestational cycle under study. Single determinations are of little value.

The technical details of the method are as follow: a four-fold extraction of the urine with normal butyl alcohol; evaporation to dryness under reduced pressure of the combined butyl alcohol extracts; solution of the residue in 0.1 N solution of sodium hydroxide; a three-fold extraction with butyl alcohol; evaporation to dryness under reduced pressure of the combined butyl alcohol extracts; precipitation by acetone of an aqueous solution of the residue; reprecipitation from fresh acetone; solution of the second acetone precipitate in hot 95 per cent ethyl alcohol; evaporation to dryness in a previously tared beaker; weighing of the residue; determination of melting point of the residue; calculation of the amount of steroid-complex content of total twenty-four-hour specimen of urine.

The cumbersomeness of this method is illustrated by the facts that a highly trained, efficient laboratory technician provided with adequate equipment can handle only the daily urines of 8 patients and that, since

## METHODS FOR ASSESSING CORPUS LUTEUM FUNCTION

Numerous methods for determining the levels of corpus luteum activity exist. None is ideal for clinical application.

1. *Bio-assay Studies*.—These have yielded disappointingly few positive data. The reason is obvious: the specific pharmacologic potency of progestin is exhausted to a great degree by the time its products filter through the kidney. The result has been that urinary extracts yield little or no progestational activity when tested by diverse techniques: (a) the Corner-Allen rabbit method;<sup>2</sup> (b) a method which measures progestin's antiestrogenic, vaginal effects;<sup>3</sup> (c) the bitterling ovipositor test;<sup>4</sup> and (d) one which employs the intrauterine application of the extract to increase its sensitivity.<sup>5</sup>

2. *Vaginal Smears*.—The microscopic study of repeated vaginal spreads, suitably stained, has been described as indicating the occurrence of significant cytologic alterations during the menstrual cycle. Some clinicians are quite enthusiastic over this method as a diagnostic aid in quantifying estrogenic and progestational levels. Most gynecologists have not been able to secure by this method clear-cut diagnostic data which were translatable to the individual patients seen in their practices. The vagaries of the patient, in part due to vaginal and cervical infections, often render prolonged studies necessary to segregate pertinent fluctuations. Critical correlational studies of vaginal cytology with other objective manifestations of the menstrual cycle are altogether too few. The method has not been applied to the determination of progestin levels during gestation.

3. *Basal Temperatures*.—Reports have appeared which suggest that significant alterations occur cyclically in basal temperatures, ovulation occurring at the time when the lowest temperatures prevail. Sufficient data are not available to permit just evaluation of this method for diagnosis of ovulation and, as a corollary, of corpus luteum function. One fears that a simple method, such as temperature taking, will not prove the solution to this diagnostic problem. Obviously this method would not be applicable to the grading of progestin levels during gestation.

4. *Endometrial Studies*.—The technique of endometrial biopsy is the only one of these methods which has permitted the practical acquisition of pertinent diagnostic data with regard to the level of ovarian function. The method obviously cannot be used during gestation.

When biopsies are secured within the first twelve to eighteen hours after the onset of bleeding, the endometrium usually serves quite reliably as a mirror of the total endocrine influences operative during the antecedent cycle. All data of this character deal with past history: they do not predict the future. When 2 or more consecutive ovarian cycles have been of anovulatory type, i.e., bleeding has occurred from estrogenic endometria, it is compatible with reasonably accurate clinical thought to assume that the immediate future cycles, unless modified by therapy, will be of the same order. When specimens of endometrium are secured from 2 or 3 sites of the uterine lining at each examination, the criticism of inadequate sampling in part is circumvented.

Grading of the progestational response at the end of the cycle is possible, when biopsies are taken at the onset of bleeding. The degree of progestational response may indicate roughly the level of progestin secretion; it must be remembered, however, that this is modified also by



Endometrial responses: P- (5 patients); P (10 patients).

Total Preg. determinations for group: 232.

Range of number of determinations per patient: 8 to 32.

Range of total amounts of Preg. recovered per patient: 20 to 173 mg.

Per patient average of total cyclic output of Preg.: 49.4 mg.

Range of times of first appearance of Preg.: 6th to 25th day of cycle.

Range of times of disappearance of Preg.: 1st to 5th day prior to bleeding.

*2a. Those Whose Bleeding Was Excessive or Prolonged and Whose Endometriums Were Irregularly Proliferated.—*

Number of patients: 3.

Endometrial responses: M- (1 patient); M (2 patients).

Total Preg. determinations for group: 40.

Range of number of determinations per patient: 8 to 16.

Range of total amounts of Preg. recovered per patient: 8 to 135 mg.

Per patient average of total cyclic output of Preg.: 51.3 mg.

Range of times of first appearance of Preg.: 10th to 22nd day of cycle.

Range of times of disappearance of Preg.: 1st to 5th day prior to bleeding.

*2b. Those Whose Bleeding Was Excessive or Prolonged and Whose Endometriums Were Regularly Proliferated.—*

Number of patients: 4.

Endometrial responses: P- (2 patients); P (2 patients).

Total Preg. determinations for group: 73.

Range of number of determinations per patient: 12 to 25.

Range of total amounts of Preg. recovered per patient: 7 to 51 mg.

#### B. 1. GYNECOLOGIC PATIENTS, WHO BLED FROM ESTROGENIC ENDOMETRIUMS AND WHO EXCRETED PREGNANEDIOL

*1. Those Whose Bleeding Was Cyclic.—*

Number of patients: 7.

Total Preg. determinations for group: 133.

Range of number of determinations per patient: 14 to 25.

Range of total amounts of Preg. recovered per patient: 14 to 118 mg.

Per patient average of total cyclic output of Preg.: 50.4 mg.

Range of times of first appearance of Preg.: 5th to 29th day of cycle.

Range of times of disappearance of Preg.: 1st to 3rd day prior to bleeding.

*2. Those Whose Bleeding Was Excessive or Prolonged.—*

Number of patients: 3.

Total Preg. determinations for group: 49.

Range of number of determinations per patient: 15 to 17.

Range of total amounts of Preg. recovered per patient: 14 to 51 mg.

Per patient average of total cyclic output of Preg.: 38 mg.

Range of times of first appearance of Preg.: 13th to 27th day of cycle.

Range of times of disappearance of Preg.: 5th to 6th day prior to bleeding.

Per patient average of total cyclic output of Preg.: 25.2 mg.

Range of times of first appearance of Preg.: 15th to 24th day of cycle.

Range of times of disappearance of Preg.: 1st to 2nd day prior to bleeding.

four days are required for the completion of the quantitation on any one specimen, five days elapse from the time collection of a twenty-four-hour specimen of urine is begun until the final report on its pregnanediol-complex content is obtained.

All patients investigated had had complete gynecologic and endocrine surveys which included, as minimal requirements, basal metabolic determinations, roentgenograms of the sella and roentgenographic estimation of osseous age, when this was pertinent. Careful menstrual data were kept. Endometrial biopsies were done at the onset of all episodes of bleeding which terminated cycles studied by pregnanediol titers. Studies of vaginal smears or basal temperatures were not made.

#### ANALYSIS OF DATA

The clinical data comprising this study represent a fair sample of our total work; they embrace the results of quantitations of 2,193 twenty-four-hour specimens of 102 patients. These represent 30.8 per cent of all determinations done. The number of patients reported is equal to 43.7 per cent of those studied. The data excluded were those obtained upon patients in whom biopsies of the endometriums were lacking and during nongestational cycles in which various treatments were being administered; otherwise, no preferential selection of data for this study was made.

In the reporting and discussion of the data secured from our studies, we have used the simple term "pregnanediol" to mean sodium pregnanediol glucuronide. Our determinations are reported in terms of milligrams of sodium pregnanediol glucuronide, the compound actually extracted from the urine, rather than in terms of milligrams of actual pregnanediol. Venning and her group have reported their findings in terms of free pregnanediol.

A detailed summary of the pertinent data on the 102 patients studied follows:

##### A. 1. GYNECOLOGIC PATIENTS, WHO BLED FROM PROGESTATIONAL ENDOMETRIUMS AND WHO EXCRETED PREGNANEDIOL

###### 1a. *Those Whose Bleeding Was Cyclic and Whose Endometriums Were Irregularly Proliferated.*—

Number of patients: 6.

Endometrial responses: M- (4 patients); M (1 patient); M+ (1 patient).

Total Pregnanediol (Preg., pregnanediol complex throughout remainder of data) determinations for group: 87.

Range of number of determinations per patient: 10 to 24.

Range of total amounts of Preg. recovered per patient: 16 to 93 mg.

Per patient average of total cyclic output of Preg.: 59.7 mg.

Range of times of first appearance of Preg.: 7th to 22nd day of cycle.

Range of times of disappearance of Preg.: 5th to 1st day prior to flowing.

###### 1b. *Those Whose Bleeding Was Cyclic and Whose Endometriums Were Regularly Proliferated.*—

Number of patients: 15.

Total Preg. determinations for group: 100.

Range of determinations per patient: 6 to 28.

### 3. *Those Past Menopause.*—

Number of patients: 6.

Total Preg. determinations for group: 86.

Range of determinations per patient: 4 to 26.

## A. 1. OBSTETRIC PATIENTS, WHO WERE STUDIED AND TREATED BECAUSE OF THREATENING ABORTIONS AND WHO SUBSEQUENTLY ABORTED OR MISCARRIED

### a. *Those Who Excreted Normal Levels of Pregnanediol.*—

Number of patients: 0.

### b. *Those Who Excreted Initially and Continually Decreased Amounts of Preg.*—

Number of patients: 3.

Total Preg. determinations for group: 65.

Range of number of determinations per patient: 12 to 39.

Range of daily Preg. values: 0 to 18 mg.

Individual schematic protocols of these patients follow:

A. N., aged 24 years, para 5-5-0, abortion at 13th week: average daily Preg. values in mg. by weeks: x,x,x,x // x,x,x<sup>+</sup>,5\* // 3,2,x,x // \*\*.

M. C., aged 23 years, para 1-1-0, abortion at 12th week: average daily Preg. values in mg. by weeks: x,x,x,x // x,x,x,x // x<sup>+</sup>,7\*,8,0, \*\*.

G. B., aged 32 years, para 0-0-0, abortion at 13th week: average daily Preg. values in mg. by weeks: x,x,x,x // x<sup>+</sup>,x\*,5,10 // 14,13,7,0 // 0, \*\*.

The symbols used in these protocols, and similar ones to follow have these significances: x, no Preg. determinations were done during the week so designated; numerals reported represent mg. of Preg. excreted daily (arranged by weeks); // indicates each interval of 4 weeks, dated from onset of last menstrual period; \* and \*\* signify, respectively, the initiation and discontinuation of antiabortional therapy; + indicates onset of symptoms of threatening abortion; ++ indicates occurrence of abortion or miscarriage; antiabortional therapy embraced use of progesterone 1 to 10 mg. daily or every other day, together with use of estrogens and of chorionic gonadotropin (at times) during first 12-16 weeks.

## A. 2. OBSTETRIC PATIENTS, WHO WERE STUDIED AND TREATED BECAUSE OF THREATENING ABORTIONS AND WHO SUBSEQUENTLY PROGRESSED TO TERM

### a. *Those Who Excreted Normal Amounts of Preg.*—

Number of patients: 1.

Total Preg. determinations: 57.

Range of daily Preg. values: 0 to 20 mg.

Schematic protocol of this patient follows:

M. Mc., aged 25 years, para 0-0-0. Average daily Preg. values in mg. by weeks: x,1,2,11 // 15,10,14\*,10 // 11,x,16<sup>+</sup>,20 // 6. R was continued to 36th week. Delivery 40th week.

### b. *Those Who Excreted Decreased Amounts of Preg.*—

Number of patients: 0.

A. 2. GYNECOLOGIC PATIENTS, WHO BLED FROM PROGESTATIONAL  
ENDOMETRIUMS AND WHO DID NOT EXCRETE PREGNANEDIOL

1a. *Those Whose Bleeding Was Cyclic and Whose Endometria Were  
Irregularly Proliferated.*—

Number of patients: 5.

Endometrial responses: M- (1 patient); M (2 patients); M+ (2 patients).

Total Preg. determinations for group: 75.

Range of number of determinations per patient: 5 to 21.

1b. *Those Whose Bleeding Was Cyclic and Whose Endometria Were  
Regularly Proliferated.*—

Number of patients: 15.

Endometrial responses: P- (7 patients); P (7 patients); P+ (1 patient).

Total Preg. determinations for group: 270.

Range of number of determinations per patient: 9 to 32.

2a. *Those Whose Bleeding Was Excessive or Prolonged and Whose  
Endometria Were Irregularly Proliferated.*—

Number of patients: 1.

Endometrial response: M.

Total Preg. determinations: 5.

B. 2. GYNECOLOGIC PATIENTS, WHO BLED FROM ESTROGENIC ENDOMETRIUMS  
AND WHO DID NOT EXCRETE PREGNANEDIOL

1. *Those Whose Bleeding Was Cyclic.*—

Number of patients: 4.

Total Preg. determinations for group: 62.

Range of number of determinations per patient: 6 to 31.

2. *Those Whose Bleeding Was Excessive or Prolonged.*—

Number of patients: 2.

Total Preg. determinations for group: 37.

Range of number of determinations per patient: 14 and 23.

C. 1. GYNECOLOGIC PATIENTS, WHO DID NOT BLEED AND YET EXCRETED  
PREGNANEDIOL

1. *Those With Intercurrent Amenorrhea (No Bleeding for Six Months  
or Longer).*—

Number of patients: 3.

Endometrial responses: not studied.

Total Preg. determinations for group: 52.

Range of number of determinations per patient: 13 to 25.

Range of total amounts of Preg. recovered per patient: 19 to 59 mg.

Per patient average of total cyclic output of Preg.: 32.3 mg.

C. 2. GYNECOLOGIC PATIENTS, WHO DID NOT BLEED AND DID NOT EXCRETE  
PREGNANEDIOL

1. *Those With Delayed Menarche.*—

Number of patients: 7.

Total Preg. determinations for group: 169.

Range of determinations per patient: 7 to 46.

2. *Those With Intercurrent Amenorrhea (No Bleeding for Six Months  
or Longer).*—

Number of patients: 9.

## Schematic protocols of these patients follow:

A. H., aged 26 years, para 3-3-0, delivery at 40th week. Average daily Preg. values in mg. by weeks: x,x,x,x // x,x,x,x // x,x,23\*,22 // 25,21,17,16 // 31,46,36,40 // 47,60,46,42 // 60,68,78,85 // 50,41,61,44 // 67,86,108\*\*,x // x,x,x,x //.

E. M., aged 26 years, para 3-2-0, pregnancy now in 32nd week. Average daily Preg. values in mg. by weeks: x,x,x,x // x\*,x,31,24 // 29,35,33,49 // 45,63,59,52 // R continued; determinations discontinued.

E. K., aged 33 years, para 5-4-1, pregnancy now in 34th week. Average daily Preg. values in mg. by weeks: x,x,x,x // x\*,x\*,x,21 // 24,10,x,14 // 28,26,30,30 // 34,33. R continued; determinations discontinued.

b. *Those Who Excreted Decreased Amounts of Preg.*—

Number of patients: 0.

## DISCUSSION

The most striking and disconcerting data encountered in these studies are those upon the pregnanediol excretion of patients whose episodes of bleeding occurred from estrogenic and progestational endometriums. Our data, when they are analyzed, yield this information:

Of the 49 patients whose cycles terminated in progestational bleeding, 21, or 42.86 per cent, excreted no pregnanediol, and of the 16 patients whose cycles terminated in estrogenic bleeding, 10, or 62.5 per cent, excreted pregnanediol.

When the average total amounts of pregnanediol excreted by those individual patients having estrogenic and progestational bleeding are calculated, these are found to be of essentially the same order: those with estrogenic bleeding 46.7 mg., and those with progestational bleeding 48.4 mg.

These findings obviously indicate that no reasonable prediction as to the nature of the endometrial response at the end of an ovarian cycle may be made from data upon the urinary excretion of pregnanediol during that cycle.

The generally established reliability of studies of endometrial biopsies in identifying the presence or absence of normal corpus luteum activity is well known in clinical practice. Therefore, we accept the endometrial data as being faithful, and we are forced to reject the pregnanediol data as being unreliable.

The question arises as to whether the patients, who failed to excrete pregnanediol during progestational cycles, have some abnormality of ovarian function. We have been unable to identify any characteristic syndrome in these patients. We have good reason to believe these patients are of normal endocrine and gynecologic status: 3 of our patients were observed to become pregnant during cycles in which no pregnanediol was excreted; the pregnancies of 2 of these progressed to term while the other patient delivered a macerated fetus at the seventh month. Certainly endometrial data indicate that failure of pregnanediol

B. 1. OBSTETRIC PATIENTS, WHO WERE STUDIED AND TREATED BECAUSE OF HISTORIES OF RECURRENT ABORTIONS OR MISCARRIAGES AND WHO SUBSEQUENTLY ABORTED OR MISCARRIED

a. *Those Who Excreted Normal Amounts of Preg.*—

Number of patients: 1.

Total Preg. determinations: 80.

Range of daily Preg. values: 3 to 62 mg.

Schematic protocol of this patient follows:

R. M., aged 30 years, para 3-3-0, miscarried at 25th week. Average daily Preg. values in mg. by weeks: x,x,x,x // x,30\*,20,11 // 10,20,22,21 // 26,29,32,38 // 50,57,x,x // x,x\*,x,x // x, \*\*.

b. *Those Who Excreted Initially and Continually Decreased Amounts of Preg.*—

Number of patients: 1.

Total Preg. determinations: 102.

Range of daily Preg. values: 0 to 42 mg.

Schematic protocol of this patient follows:

E. W., aged 26 years, para 3-3-0, miscarriage at 29th week. Average daily Preg. values in mg. by weeks: x,x,0,0 // 4,0\*,0,0 // x,x,14,12 // 24,21,15,23 // 34,31,27,28 // 26,x,x,x // x,x,x,x // x, \*\*.

c. *Those Who Excreted Essentially Normal Amounts of Preg. Until Immediately Prior to Abortion or Miscarriage.*—

Number of patients: 3.

Total Preg. determinations: 156.

Range of number of determinations per patient: 40 to 71.

Range of daily Preg. values: 0 to 80 mg.

Schematic protocols of these patients follow:

A. B., aged 35 years, para 10-10-0, miscarriage at 30th week. Average daily Preg. values in mg. by weeks: x,x,x,x // x,x,x,x\* // x,x,x,x // x,x,x,x // x,x,x,x // x,31,32,31 // 44,45,46,53 // x\*,\*\*.

(Preg. daily values fell to zero during last week of determinations.)

L. R., aged 33 years, para 3-3-0, abortion at 17th week. Average daily Preg. values in mg. by weeks: x,x,3,14 // 23,18,25,14 // 19,12\*,17,12 // 11,1,4,15\* // \*\*.

(Daily Preg. values fell to zero during 2nd and 3rd weeks before abortion.)

S. P., aged 37 years, para 6-5-1, delivery of macerated fetus at 29th week. Average daily Preg. values in mg. by weeks: x,x,x,x // x,x,x,x // x,x,x,x // x,x,x,x\* // 32,32,52,50 // 36,32,18,x // x,x,x\*,x // \*\*.

(Daily Preg. values fell to zero during last week of determinations.)

B. 2. OBSTETRIC PATIENTS, WHO WERE STUDIED AND TREATED BECAUSE OF HISTORIES OF RECURRENT ABORTIONS OR MISCARRIAGES AND WHO SUBSEQUENTLY PROGRESSED TO TERM OR ARE APPROACHING TERM

a. *Those Who Excreted Normal Amounts of Preg.*—

Number of patients: 3.

Total Preg. determinations: 263.

Range of number of determinations per patient: 42 to 154.

Range of daily Preg. values: 0 to 149 mg.

The data upon patients who did not bleed are more consistent than those upon patients who experienced bleeding cycles. Only 3 of these 25 patients, 12 per cent, excreted pregnanediol. All of these 3 patients had had intercurrent amenorrhea for 6 months or longer. The range of the total amounts of pregnanediol excreted during periods of study comparable to those of patients having bleeding cycles was of essentially the same order as for the latter patients, i.e., 10 to 59 mg.

Additional facts upon the histories and subsequent courses of these patients may explain their excretion of pregnanediol upon the basis of the existence of cyclic ovarian function: 1 had diabetes mellitus; control of this was followed by return of cyclic bleeding. One had return of cyclic bleeding from oral steroid therapy and subsequently became pregnant. One, who had not bled in 3 years, had cyclic menstrual menses. Unfortunately these observations were not controlled by studies of serial endometrial biopsies.

The fact that no pregnanediol was recovered from the urines of the 7 patients with delayed menarche and the 6 patients past the menopause may be significant. It may indicate that steroid-complexes of non-progestin origin and, therefore, not truly pregnanediol may have been recovered from the urines of the other patients with higher levels of ovarian function.

The data from studies upon the 12 obstetric patients are more consistent. All of these patients excreted some pregnanediol. Some definite but restricted correlations apparently exist between levels of urinary pregnanediol and the likelihood of abortion and miscarriage.

All of our patients whose pregnanediol values were initially and continually low subsequently aborted or miscarried despite intensive anti-abortion therapy which embraced the use of progesterone in daily doses as large as 10 mg. and combined frequently with the use of estrogens and chorionic gonadotropin.

Since in none of these patients were we able to improve the pregnanediol excretion by progestin therapy, knowledge of these low values was of no avail in arriving at correct therapeutic requirements. One of the sanguine hopes when the method first was described was that it would permit a practical application of this nature.

There was another group of patients, who, despite the excretion of normal amounts of pregnanediol during the early months of their pregnancies, ultimately aborted or miscarried. The normal pregnanediol excretionary curves of these patients during the early months of their pregnancies led to erroneous prognoses. (All were getting therapy). All of these patients, whose pregnanediol excretions were studied up until the terminations of their pregnancies, manifested, as a rule, marked decreases in these values during the week prior to abortion, some daily values always being zero. Since reports on these determinations are five days late when they come from the laboratory and since these falls in excretion

excretion is not associated with minimal progestational responses. The endometrial responses of the 21 patients in which these circumstances were present are summarized: M-, 1 patient; M, 3 patients; M+, 2 patients; P-, 7 patients; P, 7 patients; and P+, 1 patient.

In view of these facts, the assumption appears warranted that pregnanediol is not necessarily a major metabolic or excretory product of the progestin secreted from corpora lutea of nongestational cycles.

No satisfactory explanation has been found for the excretion of pregnanediol by patients with estrogenic bleeding. It is highly unlikely that these patients were having normal ovarian cycles which were not mirrored by the endometria, due, perhaps, to endometrial refractivity. Instances of this nature do occur but not with this frequency. Other findings upon these patients and their subsequent clinical courses are opposed to this theory. Refuge may be taken in the alternative that the material recovered from the urine by Venning's method might not have been sodium pregnanediol glucuronide. There are some good grounds for an assumption of this nature.

In addition to free pregnanediol and sodium pregnanediol glucuronide, Marker and his group<sup>9</sup> have found other members of the pregnane-group in the urine of normal and pregnant women: pregnanol-3( $\alpha$ )-on-20, "epipregnanolon"; allo-pregnanediol-3( $\alpha$ )-on-20, "epi-allo-pregnanolon"; allo-pregnanediol-3( $\alpha$ )-20( $\alpha$ ); and allo-pregnanediol-3( $\alpha$ )-20( $\alpha$ ). The third one of these compounds has a melting point close to that of pregnanediol and as many as 7 mg. of it have been found in a liter of pregnancy urine. Westphal<sup>10</sup> calling attention to the preceding studies cautions that pregnanediol should not be regarded as the only compound with 21 carbon atoms which results from the reduction of progesterone. Qualitative studies of progestin metabolism may prove eventually to be far more productive and instructive than quantitative ones.

The inconsistencies between the times of first appearance of pregnanediol in the urine during ovarian cycles and its times of disappearance prior to bleeding lend little support to its correlation with the formation of progestin by the corpus luteum.

In view of the foregoing observations, there is little reason to anticipate the existence of significant relationships between the degree of progestational reaction of endometria and the amount of pregnanediol excreted during associated cycles. These data confirm this lack of correlation: average total pregnanediol output of patients bleeding cyclicly from irregularly proliferated progestational endometria, 59.7 mg.; of those bleeding cyclicly from regularly proliferated progestational endometria, 49.5 mg.; of those bleeding excessively or prolongedly from irregularly proliferated progestational endometria, 51.3 mg.; and of those bleeding excessively or prolongedly from regularly proliferated progestational endometria, 25.2 mg.



daily values dropping to zero seven to ten days prior to termination of pregnancy. Since these accidents to pregnancies occurred despite intensive progesterone therapy, these data on pregnanediol excretion were of no clinical value in gauging dosage levels.

The following conclusions are held warranted from the foregoing data: (1) Venning's method is unreliable as a diagnostic aid in gynecology; and (2) the data supplied by it in obstetrics at present permit no effective therapeutic endeavors, and while these may be of prognostic import, their belated warnings are often at variance with the prognosis suggested by earlier data.

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occurred despite intensive therapy, these delayed and revised prognostic data were of no practical or constructive import.

The converse to the foregoing observations has been found true: no patients who continually excreted normal amounts of pregnanediol aborted or miscarried.

Therefore, while these obstetric data warrant the assumption that pregnanediol, as measured by Venning's method, is likely a major and significant product of chorioplacental activity and metabolism, they do not delineate a practical application for the method in clinical obstetrics. It does little good to know that an abortion or miscarriage is imminent, if appropriate and effective therapeutic schedules cannot be put in force.

#### SUMMARY AND CONCLUSIONS

Results of a four-year study designed to evaluate Venning's pregnanediol method as a practical and trustworthy aid in the diagnosis of progestin levels in gynecologic and obstetric practice are reported. Data upon quantitations of 2,193 twenty-four-hour urines of 102 patients (90 gynecologic and 12 obstetric) are analyzed.

When correlations with studies of endometrial biopsies terminating ovarian cycles investigated by pregnanediol determinations were made, it was found that of 49 patients, whose episodes of bleeding occurred from progestational endometriums, 21, or 42.86 per cent, *excreted no pregnanediol* and that of 16 patients, whose episodes of bleeding occurred from estrogenic bleeding, 10, or 62.5 per cent, *excreted pregnanediol* in amounts of the same order as those excreting it in association with progestational bleeding. Some possible explanations of these variabilities are discussed.

More consistent data were secured on 25 patients who had no bleeding cycles. All of the 7 patients with delayed menarche and all of the 6 patients past menopause excreted no pregnanediol. Three of the 12 patients with intercurrent amenorrhea, however, excreted pregnanediol. The clinical records of these patients suggest the likelihood that these had cyclic ovarian functions.

No consistent relationships were identified between the curve of pregnanediol excretion and the predicated luteal phase of the cycle or between the degree of progestational proliferation of the endometrium and the amount of pregnanediol excreted.

The data upon the 12 obstetric patients were quite consistent. All excreted pregnanediol. The four patients, whose pregnancies progressed to term, despite either histories of recurrent abortions or intercurrent threats to abort, excreted normal amounts of pregnanediol. In 7 of the remaining 8, who aborted and miscarried, studies were continued sufficiently long to be significant. The pregnanediol excretions of these were either initially and continually low or became decreased with some

cent of the end point figure recorded. Using this technique with our colony and with our criteria for interpreting smears, we have obtained practically uniform standardization values for the three crystalline estrogens in 12 assays of each that have been performed during the last three years. With 0.1  $\gamma$  of crystalline estrone as the international unit, we find 1 I.U. in 0.1  $\gamma$  of crystalline estriol and in 0.01  $\gamma$  of crystalline estradiol.

In calculating the number of micrograms of estrogenic substance in urines, these standardization values are used, and it is assumed that all of the potency of each fraction is accountable to the specified estrogen. Although our present knowledge and the accuracy of the methods do not entirely justify this procedure, a much closer approximation of the amount of estrogen excreted results than if activity units alone are recorded. A considerable amount of investigation has convinced us that the methods of extraction and assay employed in these studies are as good as any available and sufficiently quantitative to yield results of physiologic significance.

The accuracy of all urine collections was checked by determination of creatinine.<sup>3</sup> Specimens were kept cold during the period of collection and extracted within twelve hours of the last voiding.

#### EXPLANATION OF TERMS

$T_o$  symbolizes the total urinary estrogens excreted as such, that is, the total estrogenic potency of the urine after hydrochloric acid hydrolysis. It is the sum of the activities of the estradiol, estrone, and estriol fractions and is expressed in activity units (international units or estrone equivalents).

$T_{zn}$ , also expressed in activity units, symbolizes the total estrogenic potency of the urine after prolonged hydrochloric acid hydrolysis in the presence of powdered zinc. This procedure has been shown<sup>2</sup> to convert any estrone in the urine into some compound approximately five times as active as estrone, to have no effect upon the potency of estradiol or estriol, and to render estrogenically active certain urinary constituents which are excreted in an inactive form and which are not rendered estrogenic by simple hydrochloric acid hydrolysis. "Unaccounted for"  $T_{zn}$  activity, therefore, is the difference between the total  $T_{zn}$  value and the sum of the potencies of the estradiol, estriol, and five times the estrone fractions.

#### EXPERIMENT

The subject, Miss M., aged 50 years, and in excellent health, had undergone supravaginal hysterectomy with bilateral salpingo-oophorectomy nearly eight years previously. She had taken estrogenic substances intermittently until one month before the inception of this study, the results of which are presented in Table I. Three days after the injection of estrone a series of severe hot flushes supervened.

The seventy-two-hour control specimen contained 90 I.U. of estrogenic activity, which was located in the estradiol fraction. Small amounts of estrogenic activity in menopausal urine have been reported before and assumed to come from the adrenal glands.

During the three days following the injection of 5 mg. of estrone, 3,350 I.U. were recovered, 64 per cent as estradiol, 19 per cent as estriol, and

# CLINICAL EXPERIMENTS IN RELATION TO THE EXCRETION OF THE ESTROGENS\*

## I. URINARY ESTROGENS BEFORE AND AFTER THE INJECTION OF ESTRONE INTO A PATIENT WITH SURGICAL MENOPAUSE

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THIS and the following studies represent some of our efforts during the past two years to learn more about the metabolism of the sex steroids both in normal women, in those with functional disorders, and in those with pregnancy toxemia.

### METHODS

The technique utilized for hydrochloric acid hydrolysis of urine, for extraction and separation of the estrogens, and for zinc-hydrochloric acid hydrolysis were the same as previously published.<sup>1, 2†</sup> Special precautions must be taken against loss or destruction of estradiol during semicarbazide treatment of the estrone-estradiol fraction. The whole procedure is carried out in a single receptacle. The evaporation after semicarbazone formation is performed in vacuo and alcohol is added immediately, since estradiol is rapidly destroyed in concentrated acid solution. Since the difference in estrogenic potency of this fraction before and after the semicarbazide procedure is the estrone value, any loss of estradiol would give a falsely high figure for estrone. Assay by difference is open to objection, especially when bio-assay must be used, but we have found this method more dependable, when small amounts of estrone are present, than Girard's separation and assay of the separated fractions.

Assays were performed upon mature-spayed rats of known reactivity to a standard dose of crystalline estradiol (0.1  $\gamma$  in 0.1 c.c. of olive oil in one injection) and maintained in a primed condition by the induction of estrus (by test or a priming injection of estradiol) once in every seven to ten days. Each animal used for testing an unknown was in estrus five days previously. The material for a given assay was injected in three subcutaneous doses (0.1 to 0.2 c.c. of olive oil per injection) four hours apart and vaginal smears were taken forty-eight hours from the first injection. One rat unit (5 I. U. by our assay) was considered present in that dosage of the extract which produced positive smears in 4 of 6 rats or in 50 per cent of 8 or more rats, provided no more than 25 per cent of 8 or more rats showed positive smears at the next lower dosage. The difference between dosage levels introduced a range of values over which the end point might lie, amounting to 10 to 25 per

\*This and the three papers on this subject to be published in succeeding issues were presented in brief before the New York Obstetrical Society on Jan. 13, 1942.

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†The references will accompany the fourth paper of this series.

17 per cent as estrone. In terms of activity, 6.7 per cent of the injected material found its way into the urine. This figure agrees with reported urinary recovery of injected estrone in dogs.<sup>4, 5</sup> In terms of weight, however, only 2.8 per cent of the injected estrone was recovered, 15 per cent as estradiol, 40 per cent as estrone, and 45 per cent as estriol. After zinc-hydrochloric acid hydrolysis, 10,150 I.U., 20.3 per cent of the injected material in terms of potency, were recovered. Fifty-six per cent (5,650 I.U.) of this total  $T_{zn}$  activity came from the estrogens present before zinc-hydrochloric acid hydrolysis, as explained in the footnotes of the table, leaving 4,500 I.U., or 44 per cent, unaccounted for.

#### DISCUSSION

If urine had been collected for another day following injection a little more estrogenic activity would probably have been recovered, but not enough to alter significantly the presented figures. From reports now appearing<sup>4, 5</sup> and our own as yet incomplete data, it is certain that some, less than 10 per cent, of the administered hormone was excreted in the bile and possibly through the intestinal mucosa.

We have repeatedly presented evidence<sup>6-11</sup> that estrone to estriol conversion is a gauge of progestin activity, but this subject following injection of estrone excreted a goodly amount of activity in the estriol fraction in the absence of any known endogenous progestin. However, we have also demonstrated that administered testosterone and adrenal cortical extract act like progesterone in inhibiting destruction and enhancing conversion of estradiol to estrone to estriol.<sup>7, 10</sup> Furthermore, we have found that pregnanediol glucuronidate, a physiologically inert excretion product of progesterone, augments the effect of progesterone upon estrogen metabolism, through protecting progesterone against destruction.<sup>10</sup> It begins to appear that retardation of steroid degradation may be the primary factor in the conversion mechanism. Thus, in the present experiment, the quantity of estrone administered may itself have clogged the estrogen destructive process enough to permit estrone to estriol conversion, or it may have had the same final effect indirectly through protecting adrenal steroids from destruction. That the high level of estrogen was either directly or indirectly preventing degradation is indicated by the difference in partition of urinary metabolites during the first twenty-four hours after injection, when total estrogens were high, and the last forty-eight hours, when the excretion per twenty-four-hour volume was one-fourth as great. In the second specimen, evidence for a marked increase in the rate of estrogen destruction is found in the drop in estrone and rise in  $T_{zn}$  to  $T_o$  ratio. The rate of estriol excretion decreased only 50 per cent during the last forty-eight hours, as compared with a 90 per cent drop in estrone, an observation which is in keeping with the known stability of estriol as compared with estrone to oxidative destruction.

TABLE I. MISS M. SURGICAL CASTRATE. URINARY ESTROGENS BEFORE AND AFTER INJECTION OF ESTRONE

|   |      | URINARY ESTROGENS AFTER HCl HYDROLYSIS |                |               |               | URINARY ESTROGENS AFTER Zn-HCl HYDROLYSIS |                     |                      |                                 |
|---|------|--|----------------|---------------|---------------|---|---------------------|----------------------|---------------------------------|
|   |      | TOTAL (T <sub>o</sub> )                | ESTRADIOL      | ESTRONE       | ESTRIOL       | TOTAL (T <sub>zn</sub> )                  | FROM T <sub>o</sub> | UNAC-<br>COUNTED FOR | T <sub>zn</sub> /T <sub>o</sub> |
| 72°<br>control<br>2/3-6/41  | I.U. | 90                                     | 90<br>(100%)   | 0             | 0             | 135                                       | 90<br>(67%)         | 45<br>(33%)          | 1.5                             |
|   | γ    | 0.9                                    | 0.9<br>(100%)  | 0             | 0             |   |                     |                      |                                 |
| 5.0 mg. (5,000 γ or 50,000 I.U.) Estrone (Parke, Davis & Co. Theelin in oil) I.M. |      |  |                |               |               |   |                     |                      |                                 |
| 2/10/41   |      |  |                |               |               |   |                     |                      |                                 |
| First 24°<br>after inj.<br>2/10-11/41   | I.U. | 2,250                                  | 1,450<br>(65%) | 475*<br>(21%) | 325<br>(14%)  | 4,350                                     | 4,150†<br>(95%)     | 200<br>(5%)          | 1.9                             |
|   | γ    | 94.5                                   | 14.5<br>(15%)  | 47.5<br>(50%) | 32.5<br>(35%) |   |                     |                      |                                 |
| 48°<br>24-72°<br>after inj.<br>2/11-13/41   | I.U. | 1,100                                  | 700<br>(64%)   | 100<br>(9%)   | 300<br>(27%)  | 5,800                                     | 1,500‡<br>(26%)     | 4,300<br>(74%)       | 5.3                             |
|   | γ    | 47.0                                   | 7<br>(15%)     | 10<br>(21%)   | 30<br>(64%)   |   |                     |                      |                                 |
| Total 72°<br>recovery<br>after<br>injection<br>2/10-13/41                         | I.U. | 3,350<br>(6.7%)                        |                |               |               | 10,150<br>(20.3%)                         |                     | 4,500<br>from        |                                 |
|   | γ    | 141.5<br>(2.8%)                        |                |               |               |   |                     |                      |                                 |
| 5,000 minus 141.5 = 4,860 γ or 48,600 I.U. lost estrone ←                         |      |  |                |               |               |   |                     |                      |                                 |

\*This value, obtained by difference in potency before and after semicarbazide treatment of the estrone-estradiol fraction, was confirmed by performing a separation with Girard's reagent.

†Zinc-hydrochloric acid hydrolysis of the ketonic fraction after Girard's separation (474 I.U. estrone) yielded 2,375 I.U., a fivefold increase in potency.‡ Therefore, of the total 4,350 I.U. after zinc-hydrochloric acid hydrolysis of the urine itself, 2,375 I.U. were derived from estrone and 1,775 I.U. from estradiol and estriol, neither of which is affected by zinc-hydrochloric acid hydrolysis.

‡Similarly, this value is the sum of 700 I.U. estradiol, 300 I.U. estriol, and 5×100 I.U. estrone.

## THE HISTOPATHOLOGIC DIAGNOSES OF THE ATYPICAL ENDOMETRIUM\*

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IT IS the avowed purpose of far-seeing pathologists and clinicians to make their objective that stated by Virchow many years ago, namely "a functional interpretation of their pathologic findings." At present this is impossible in many instances, for example when the tissue studied represents an end stage of a process which has passed through many intermediate phases long lost to view, as in a kidney showing advanced chronic glomerulonephritis. In other instances as in the differential diagnosis of various varieties of appendicitis, the desirability or necessity of such a functional objective does not appear important. In recent years, however, in one field, namely in the diagnosis of the non-neoplastic endometrial states, the attempt to correlate functional status with histologic appearances has been consciously sought for and in some measure achieved. It is because of this attempted and moderately successful correlation between histologic character and functional status that the detailed study of the endometrium is of importance and certain inadequacies of diagnosis become apparent.

It is considered sufficient in general in making pathologic diagnoses to call attention to the dominant pathologic finding and neglect the remainder. In many cases of focally acute appendicitis and in many other nondiffuse pathologic states, as in patchy nephrosclerosis, the existence of normal areas are implied and understood though not explicitly stated and probably no great harm to understanding and practice result. But the requirements of diagnoses appear quite different in regard to the endometrium. In the appraisal of the pathologic status in perhaps no other tissue does a complete, detailed and co-ordinated survey appear so important as in the study of the endometrium. Too frequently the pathologist, habituated to specific diagnoses or to the clinicians' impatience with anything but such specific and final diagnoses, permits himself this indulgence though he often so does with misgivings and doubt. The facts are that the character of many endometriums does not permit specific all inclusive diagnoses and such diagnoses are in many instances misleading or, at best, inadequate. Sometimes in an effort to salvage the situation the term diplastic is used, in the hope that an amplification of the term will be asked for and its inadequacies rectified.

\*Read at a meeting of the Obstetrical Society of Philadelphia, March 5, 1942.

The thesis that the partition of urinary estrogens provides an index of progestin activity, therefore, must be modified, especially when ovarian and placental secretions are absent or are not the predominating factors in steroid metabolism. In the nonpregnant female with active ovaries, however, and in pregnancy the thesis still holds, as demonstrated by the urinary findings after administration of progesterone (see second paper of this series), during the luteal phase of ovulatory cycles,<sup>6, 11</sup> and third paper of this series and the parallel curves of estriol and pregnanediol in pregnancy.<sup>8-10</sup> Contrary to our previous assumptions,<sup>6</sup> based on the work of Pincus and Zahl,<sup>12, 13</sup> the uterus is not necessary for estrone-to-estriol conversion and the ovaries are not needed for the reversible estrone-to-estradiol reaction.

Acid hydrolysis of urine with the addition of powdered zinc has in our studies consistently given higher estrogenic activity than acid hydrolysis alone. We have shown that this procedure does not change the activity of estradiol or estriol but results in about a fivefold increase in the potency of estrone, ascribable to conversion of this ketone into estradiol, probably a mixture of the  $\alpha$  and  $\beta$  forms.<sup>2</sup> The method, however, yields more estrogenic activity than can be accounted for even by maximum conversion of estrone, and this we have designated "unaccounted for." Although more complete hydrolysis with the longer boiling period of the zinc-hydrochloric acid procedure may contribute to this fraction, we have considerable evidence in favor of the assumption that resynthesis of estrogenic substance from inactive estrogen metabolites is the source of a large part of it, especially in urines with high  $T_{24}$  to  $T_0$  ratios.<sup>2</sup> Certainly in the present experiment the 4,500 I.U. of "unaccounted for" activity must have come from the injected estrone and at that represents only about 9 per cent of the lost activity.

#### CONCLUSIONS

From this experiment we would conclude that in the castrate female: estrone is converted in the body both to estradiol and estriol; this conversion mechanism is favored by retardation of steroid degradation; the internal genitalia are not necessary for these processes; less than 3 per cent by weight of injected estrone reaches the urine in recognized forms; hydrolysis with the addition of zinc recovers more of the injected estrogen, a finding consistent with our hypothesis that a good part of the additional activity from zinc-hydrochloric acid hydrolysis represents rehydrogenation of inactive products of estrogen oxidation.



prepare material and facts for further clinical evaluation when our knowledge and insight increase.

Figs. 1 and 2 illustrate the variability of the histologic pattern in some endometriums.

Many studies have testified to our present inability to correlate clinical symptoms with tissue findings, though the latter is generally admitted to be as valuable as any single method of investigation at present available. Thus there have been observed the association of hyperplastic tissue with both amenorrhea and menorrhagia, and we and others have

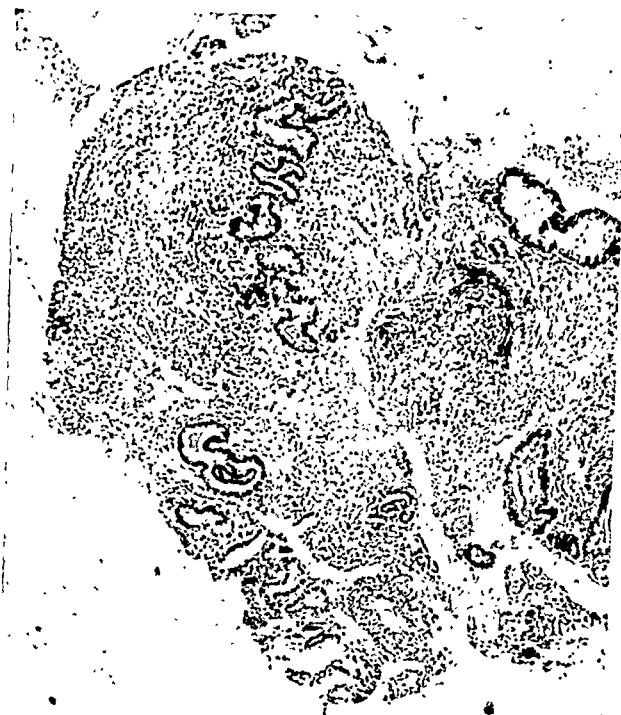


Fig. 1.—Patient, aged 32 years, had a prolonged menstrual bleeding. Area shows scarring and a few glands ( $\times 43$ ).

observed secretory features in a generally hyperplastic tissue. Menorrhagia associated with secretory types of endometrium have been noted and particularly commented upon by Traut and Kuder.<sup>1</sup> Such findings, as these and others, cannot as yet be fitted into any consistent and simple physiologic or pathologic scheme except by some tortured interpretation or by assumptions which cannot at present be either substantiated or discredited.

In such a state of affairs it would appear more commendable to reveal rather than conceal our inadequacies by describing the findings and by not attempting unwarranted diagnoses. Because of such considerations one wonders whether the use of the biopsy technique may not be contributing in some measure to our present and future deficiencies in

For this undesirable situation there appears to be but two satisfactory solutions. The first and less satisfactory is to give as detailed a written description of the findings as possible in the hope that the description will be read. The second and the more satisfactory solution is to supplement this description with a personal study of the slide by the qualified clinician either alone or in collaboration with the pathologist. In this day of certification by Diplomate Boards, histologic knowledge is becoming an increasingly frequent acquisition by the gynecologist.

Even were the above-outlined objective achieved, the study of the endometrium by the pathologist and clinician in their attempt to arrive at a satisfactory opinion would suffer from a number of other possible limitations. Clinicians, more or less experienced, differ in the thoroughness with which they practice curettage and in the endometrial sites they are likely to explore. The same patient may yield different quantities and kinds of material in the hands of different gynecologists. Since as a result the tissue submitted may not be sufficiently variable and representative, and since the pathologist is to some extent dependent for his opinion upon the mere quantitative as well as qualitative aspects of the curettage, he may be misled. Thus focal hyperplasia may be present in an endometrium otherwise atrophic so that the pathologist observing hyperplastic areas would hesitate to make a diagnosis of unqualified hyperplasia when only a small amount of scrapings have been obtained at the curettage. Again, some clinicians do not record very precisely the amount of material they obtain, making the pathologist completely dependent for his quantitative estimate on the amount submitted for examination. This dependency too may fail the pathologist since it is the practice of some operators not to send all the scrapings they obtain to the laboratory but instead to select, often at random, portions for examination. This latter practice is undesirable since it substitutes a hurried, often capricious choice for the presumably unhurried and in some instances better qualified choice by the pathologist.

The considerations discussed above become important because of the lack of uniformity of the appearance of different portions of the endometrium under certain conditions. The proper status of the endometrium should be appraised on both quantitative and qualitative grounds. It is a matter of conjecture whether a hypoplastic but otherwise adequately secretory endometrium, is adequate for nidation. Should a small or moderately large focus of hyperplasia be accepted as the cause of bleeding in an otherwise normal endometrium, remembering of course that there is as yet no definitive opinion concerning the relationship between bleeding and hyperplasia? Does a relatively small focus of secretory endometrium in an otherwise hyperplastic tissue reflect the possibilities of successful nidation? Whatever the answers to these questions, the immediate clinical problem is certainly not advanced by merely listing an over-all diagnosis nor are we in this manner likely to

## DISCUSSION,

DR. F. SIDNEY DUNNE.—I believe the question of an endometrial biopsy is done with only one intention most of the time, namely to give the clinician or pathologist the information whether the patient is ovulating. It is well proved that endometrium ripens irregularly, so that you may have a rather confusing picture in interpreting a whole block of curettings. What is often taken to be premenstrual change is not a true endometrial change. It is classified as a pseudo-stratification or a gland cut on the diagonal which may be interpreted as premenstrual change. It is not unusual to find in a well-developed endometrium cystic glands which cannot be termed hyperplasia in the sense that the word is used. It does mean a definite clinical entity and you can have a well-developed hyperplasia.

I think the study of endometrium depends on the serial section, but we have no way of drawing conclusions to help the clinician as to where this pocket endometrial pattern has its clinical symptoms. You can have any type of endometrium which may give amenorrhea, menorrhagia, or oligomenorrhea. The thing we are getting at is interpretation of endometrial changes in the entire block, and try to interpret other areas which do not fit in with the menstrual history. We still have a lot to learn in interpreting endometrial patterns. It is not unusual to have normal endometrium falsely diagnosed as carcinoma or many other things, but the important thing is you may have a variety of histologic appearances in any group of endometrial curettings and turn back nothing to help the clinician.

We still have not reached the point where we can correlate endocrinology with our pathology.

## USE OF SULFANILAMIDE POWDER IN GYNECOLOGIC AND OBSTETRIC OPERATIONS

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**R**ECOGNITION of the principles governing the action of sulfanilamide led logically to its application directly to the tissues which need its effects most. Lockwood<sup>11</sup> enunciated these principles clearly when he stated that it works best when:

1. The supply of phagocytes is richest, such as in the peritoneum;
2. The greatest concentrations are in actual contact with the bacteria;
3. There is not much necrotic tissue present, with its protein digestion products which are capable of immobilizing the sulfanilamide molecules.

Therefore, the chief indications for the use of sulfanilamide powder in obstetric and gynecologic operations are:

1. Peritonitis, regardless of the causative organisms or the presence of gastric or intestinal contents;
2. Contamination of the peritoneal cavity at operation, either by opening this normally sterile cavity into continuity with a normally infected cavity, as for example, the vagina, or by trauma to, or removal of, infected tissues or organs such as pyosalpinges;

knowledge. The biopsy technique has, of course, its legitimate applications, but those of us who have seen one small focus of decidua or adherent groups of chorionic villi, in an otherwise undistinguished endometrium or those of us who have been impressed with the variability of endometrial pattern in some endometriums, cannot but feel that frequently the study of only the small pieces obtained by this method, must in some degree be inadequate.



Fig. 2.—Same case as in Fig. 1, showing normal secretory endometrium ( $\times 65$ ).

#### SUMMARY

Attention has been called to the variability of the histologic findings in different portions of curettings removed for various clinical conditions, and hence the necessity of utilizing as frequently as possible the procedure of curettage rather than that of biopsy.

Because of the present inadequate state of our knowledge and because of our inability to satisfactorily correlate many histopathologic findings with the hormonal status of the patient or with the inherent responsiveness of the endometrium, it is felt inadvisable in many instances to attempt all inclusive specific diagnoses. It is considered more advisable in these cases to restrict one's self to full descriptive reports supplemented by consultation and discussion between clinician and pathologist, in the hope that the future may bring clarification and unity to these objectively recorded findings.

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the uterus and in the lateral parts of the pelvis. In extraperitoneal types, it was put into the tissue spaces opened for the delivery of the child. It was used more often in cases of prolonged labor with ruptured membranes than in ordinary cases, the average elapsed time before section in the cases where sulfanilamide was used being twenty-seven hours' labor and thirty hours with ruptured membranes, while for the cases where sulfanilamide was not used, the figures were fourteen and seventeen hours, respectively. Elective sections are not included in these averages. Only four classical sections were done at the Woman's Hospital in the period covered by this study.

In vaginal plastic operations, the powder was put under the vaginal flaps, and into the peritoneum whenever the latter was opened. In tubo-ovarian abscesses, the powder was applied about the areas where the infection was thought most likely to have been spread. For comparison with these cases, similar types of operations from the work of the same year were taken. Although the comparison is not quite accurate, due to the tendency to use sulfanilamide in the more serious cases, and leave it out in the less serious, still it is of interest to note that some of the principles outlined above were as well borne out as could be expected in a series of this length. The mortality, the number, and the seriousness of the complications, the wound healing and the fever were used as criteria for evaluating the patients' toleration of the drug and the operative procedure. If the temperature rose to 100° F. or above at any time during the twenty-four hours, the day was counted as a day of fever. Temperatures were taken every four hours.

Among the cases of complete hysterectomy from the abdominal approach, 62 were done without sulfanilamide and 31 with sulfanilamide.

TABLE I. COMPLETE HYSTERECTOMIES

|                       | IMPERFECT WOUNDS | COMPLICATIONS | DEATHS   |
|-----------------------|------------------|---------------|----------|
| Without sulfanilamide | 4 (6.4%)         | 7 (11.3%)     | 3 (4.9%) |
| With sulfanilamide    | 3 (9.7%)         | 3 ( 9.7%)     | 1 (3.2%) |

## RESULTS

Three of the four imperfect wounds in the group without sulfanilamide were definitely infected, and the average duration of fever was nine days. In the group with sulfanilamide, none of the imperfect wounds were infected, the defects being due to fat necrosis and hematoma. In the cases where sulfanilamide was not used, the complications consisted of five urinary tract infections, one abscess of the vaginal vault, and one bronchopneumonia. Among the cases with sulfanilamide, there was one bronchopneumonia, one severe cyanosis due to sulfanilamide (this occurring in a 67-year-old hypertensive patient with nephrosclerosis), and one abscess of the vaginal vault following a complete hysterectomy done for myoma but complicated by abscesses in both tubes.

3. Prevention of formation of adhesions in cases where there is mechanical or chemical irritation or where there are large areas left unperitonealized after the removal of large tumors;
4. Abscess cavities which are opened and drained, such as a pelvic or Bartholin gland abscess.

The dosage depends upon the condition found at operation. The largest amount given is 15 Gm. in the peritoneal cavity plus four or five in the abdominal wall, but this amount is used only in severe cases of peritonitis where drainage is contemplated. Prophylaxis of peritonitis is accomplished by the use of 8 Gm. or less and it is questionable whether any should be put into the abdominal wound. The use of drainage calls for higher doses in order to allow for the escape of the powder in the drainage fluid. The presence of necrotic material and peritoneal exudates of caseous types also indicates the larger doses. The clean peritoneum absorbs the material more rapidly than the inflamed membrane, and very large doses are contraindicated in preventive applications, because toxic levels in the blood may be reached quickly.

The mode of application is not important, so long as the powder is kept dry and applied thinly and evenly. One good method is application by a sterilized insufflator, especially convenient in inaccessible places. The powder is prepared for use by heating it in tubes at 140° C. in a dry oven for two hours.

No serious local effects have resulted from the application of the powder in the doses given. The concentrations obtained in the peritoneum are found to be 75 to 100 times the blood level usually reached, and it is probably not all absorbed from the peritoneum for three days.

When a sulfa drug has been used by topical application, it is undesirable and usually unnecessary to supplement it by other methods of administration for three days afterward, and the use of oral medication of this type before operation in which it will be used intraperitoneally is inadvisable. These precautions will prevent a number of cases of chemical hepatitis, examples of which have been frequently noted, especially before these precautions were recognized as necessary. Cyanosis is frequent but less serious than hepatitis. Fever, which could be assigned to the use of the drug, and optic atrophy have also been reported after intraperitoneal application.

Our cases included complete hysterectomies, vaginal plastics, operations on tuboovarian abscesses, and miscellaneous clean cases, such as supravaginal hysterectomies and suspensions. In addition to these there were 23 miscellaneous infected cases with very serious conditions present before operation.

In the complete hysterectomies, the powder was divided between the upper end of the vagina and the cul-de-sac of Douglas. In cesarean sections, it was placed under the flap of peritoneum on the surface of

TABLE IV. TUBOOVARIAN ABSCESS

|                       | IMPERFECT WOUNDS |      |               | COMPLICATIONS |   |               | DEATHS |
|-----------------------|------------------|------|---------------|---------------|---|---------------|--------|
|                       | NO.              | %    | DAYS<br>FEVER | NO.           | % | DAYS<br>FEVER |        |
| Without sulfanilamide | 1                | 10.0 | 9             | 0             |   |               | 0      |
| With sulfanilamide    | 2                | 15.3 | 8             | 0             |   |               | 1      |

Ten cases were done without sulfanilamide and 15 with sulfanilamide. The death occurred in a woman with large bilateral tuboovarian abscesses, myomas, and peritonitis. A dose of 8 Gm. was put into the peritoneal cavity, followed by 6 doses of 1 Gm. each every four hours by mouth. On the second postoperative day, the blood level was 30 mg. The oral medication was stopped, and in forty-eight hours the level fell to 10 mg.; however, she died on the fifth postoperative day.

There were 27 patients without evidence of infection and in whom no infected cavity was opened into continuity with the peritoneum, in which sulfanilamide was used. One of these had thrombophlebitis and left lower lobe embolism, but recovered. Another whose hospital course had been normal, died at home of pulmonary embolism on the fortieth day after operation.

There remain 23 cases of miscellaneous infections in which sulfanilamide was used, bringing the total for all cases in the year to 143. The most interesting was that of a white woman of 76 years with no discernible heart or kidney lesions, but emaciated and in only fair general condition, who was admitted because of lower abdominal pain and a mass. A barium enema study showed diverticuli of the colon, but incidentally did not show gallstones. At operation, the liver felt normal, but the gall bladder was three times normal size and felt tense. No stones were palpable. The uterus contained several large myomas, and the scheduled hysterectomy was done. The patient went into shock and was given 100 c.c. of gum acacia-glucose solution intravenously. Six grams of sulfanilamide was put into the abdominal cavity. She developed increasing jaundice and fever (107° F.) and died twenty-four hours after operation. No additional sulfa medication had been given at any time.

A woman with strangulated inguinal hernia and gangrene of the intestine died after an operation in which 8 Gm. was used. Four patients with carcinoma and involvement of the bowel by the tumor or by radiation effect, all died within a few days of operation from pneumonia and peritonitis. Sulfanilamide was used successfully in three mastectomies. It was also used in six cases of appendicitis, but all those whose peritoneal culture showed the presence of bacteria in the peritoneal fluid at the time of operation, had infected wounds in spite of the sulfanilamide.

A middle-aged white woman had peritonitis of unknown origin, which involved the entire cavity equally with a thick, fibrinous exudate. The appendix was removed in the belief that it was the focus of infection, and 8 Gm. were put into the cavity and distributed equally. She developed and recovered from a bilateral lobar pneumonia, being given therapeutic doses of sulfathiazole by mouth after the second postoperative day. She had only five days of fever.

One case of pyometra showing gram-positive cocci had an infected wound following puncture of an atrophic uterus by the tenaculum. An-

There were three deaths among those without sulfanilamide, one of which was due to carcinomatosis, and two to peritonitis. There was only one death among those treated with sulfanilamide and this was due to pulmonary embolism followed by coronary thrombosis. Thus, among the cases where no infection existed before operation, there was no death from peritonitis and no abscess of the vaginal vault, when sulfanilamide was used.

Only the major varieties of plastic repairs, such as cystocele, rectocele, and lacerated pelvic floor, or continence of urine, or fistula, were considered in this series. There were 28 cases of vaginal hysterectomy in which sulfanilamide was not used, and four developed abscesses of the vaginal vault. One of these patients died from this cause. Six patients who had vaginal hysterectomies and, in whom sulfanilamide was used, all escaped without abscesses.

TABLE II. VAGINAL PLASTICS

|                       | IMPERFECT WOUNDS |     |               | COMPLICATIONS |      |               | DEATHS |
|-----------------------|------------------|-----|---------------|---------------|------|---------------|--------|
|                       | NO.              | %   | DAYS<br>FEVER | NO.           | %    | DAYS<br>FEVER |        |
| Without sulfanilamide | 12               | 8.3 | 9             | 35            | 24.4 | 8             | 1      |
| With sulfanilamide    | 1                | 6.6 | 4             | 4             | 26.4 | 8             | 0      |

Five of the 12 wounds mentioned above were definitely infected, with an average of fourteen days' fever and evidence of poor healing, including the formation of abscesses, one of which, not included in this five, is the death reported above. Among the cases where sulfanilamide was used, there was only one infected wound and no deaths. The complications were largely urinary, consisting of cystitis and pyelitis, showing *Staphylococcus albus* or *Bacillus coli* on culture, but there was also one case of bronchopneumonia and one of endometritis following a curettage and plastic operation. All the complications were urinary among the cases with sulfanilamide. A total of 143 plastics was done without sulfanilamide and 15 with it.

As previously noted there was a marked tendency to use sulfanilamide in the cases considered potentially infected. There were 111 cases in which sulfanilamide was not used and 34 in which it was used.

TABLE III. CESAREAN SECTIONS

|                       | IMPERFECT WOUNDS |     |               | COMPLICATIONS |     |               | DEATHS |
|-----------------------|------------------|-----|---------------|---------------|-----|---------------|--------|
|                       | NO.              | %   | DAYS<br>FEVER | NO.           | %   | DAYS<br>FEVER |        |
| Without sulfanilamide | 3                | 2.7 | 8             | 10            | 9.9 | 8             | 0      |
| With sulfanilamide    | 1                | 3.0 | 24            | 2             | 6.0 | 15            | 0      |

Of really infected wounds, there were two among those without sulfanilamide and one among those with sulfanilamide. The complications were mild respiratory, urinary, breast, and parametrial infections. The patient with the infected wound, in whom sulfanilamide had been used, also developed paralytic ileus, pleurisy, and thrombophlebitis. Her operation was done after she had been in labor for thirty-seven hours. The other complication was a respiratory infection.



## ORIGIN OF ENDOMETRIOSIS FROM THE MESENCHYME OF THE CELOMIC WALLS

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THE controversy about the origin of endometriosis has divided the investigators into two groups, one advocating a local origin and the other suggesting transportation of material from the endometrium. Stimulated by the rise of our knowledge of latent developmental potencies, several adherents to the former idea undertook to explain ectopic endometriosis by activation of latent potencies in cells embryologically related to the endometrium. Similarly, the present work is concerned with the application of the author's recent embryologic results to the theory of endometriosis. It should be understood that the following discussion has the sole purpose of pointing out how the origin of endometriosis in all known locations can be explained on the basis of our present embryologic knowledge. This will oppose theories of transportation of tissue cells from the endometrium only so far as they are based on the assumption that in certain locations endometriosis cannot develop from local cells. In line with this aim, only the problem of possible local origin of endometriosis will be considered in the following pages.

No detailed survey of the literature will be given, since there are numerous reviews of this subject on hand. Many investigators assume that part or all of the epithelium of the serous cavities, being the mother tissue of the Müllerian ducts, may give rise to dystopic endometrial epithelium. This theory was then extended, mainly by Heim,<sup>1</sup> to include the mesenchyme of the caudal parts of the celomic walls. This assumption was based on the fact that in the early embryo mesenchymal cells originate from the future peritoneal epithelium. However, part of Heim's considerations are embryologically ill-founded. He designates the mesenchyme of the cloacal portion of the former celomic cavity\* as a possible source of endometriosis, holding that the female genital organs develop in that area. In fact, the urogenital ridges originally reach into the thoracic region where the Müllerian ducts first appear. When finally cases of endometriosis in the extremities were found, Biehl<sup>2</sup> suggested that all mesenchyme of the body might have the potencies necessary for the formation of endometrial epithelium.

\*Author's free translation of "Mesenchym im Bereich des Kloakenabschnittes der früheren Cöloalhöhle" (Heim:<sup>1</sup> p. 303).

other patient had a foreign body removed from the abdominal cavity several days after a section. Four grams were placed in the peritoneum at the second operation, with an uneventful convalescence. A woman with a carcinoma of the fundus and postradiation adhesions had 4 Gm. placed in the abdominal cavity. The stay sutures became infected and she had a peritonitis with twenty-nine days of fever, but recovered.

A patient admitted with a postoperative vesicovaginal fistula, had one ureter implanted into the bowel, and sulfanilamide was used. She died of pulmonary embolism on the twentieth day.

A 240-pound woman with chronic gall bladder disease had a cholecystectomy and appendectomy, followed by evisceration on the fifth day. No sulfanilamide had been used at this operation, but when the wound was resutured, 16 Gm. were used. She died forty-eight hours later. Fourteen grams of powder were placed in the wounds of a combined abdominoperineal resection of the colon for radiation stricture. The patient recovered after forty-eight days of fever.

#### SUMMARY

1. A brief review of principles gleaned from the literature is presented.

2. All the cases in which sulfanilamide powder was used at operation at the Woman's Hospital during 1941 are reviewed, and only two complications due to the use of the drug were noted. One was a severe cyanosis, and the other was hepatitis, which ended in death of patient, but other factors than the sulfanilamide were operating in this case, and only 6 Gm. were used.

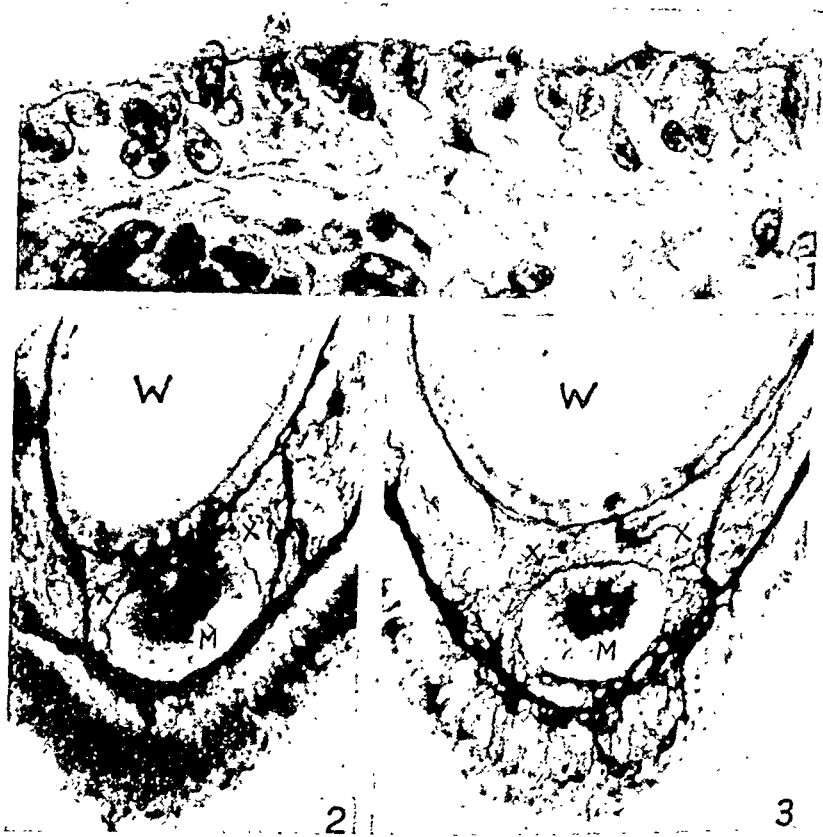
3. Prevention of abscesses at the upper end of the vagina and prevention of peritonitis are the two clear-cut objectives to be striven for in the use of the powder in complete abdominal and in vaginal hysterectomies. In our short series, progress was made toward both of these. In cases with infection, prevention of peritonitis is more difficult to evaluate, and abscess formation harder to control, due to the variability in degree and virulence of infection and amount of spill.

4. Sulfanilamide did not prevent urinary, respiratory, nor circulatory complications, nor did it rescue moribund patients. Its use cannot obviate the need for good judgment and early treatment.

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of the Müllerian ducts, namely, the celomic walls. This includes not only the epithelium of the serous membranes, but also the underlying connective tissue and the organs formed by these tissues in the embryo. No definite boundaries of the connective tissue of the celomic walls against that of other origin (somites, etc.) can be given. As indicated above, we have no reason to restrict the area of possible endometrial



Figs. 1 to 3.—Mesenchyme formation from the lining of the colomic cavity and from the Müllerian duct (after Gruenwald<sup>3</sup>).

Fig. 1.—Celomic wall of a human embryo of the third week. Hemalum-eosin stain. No epithelium is present. The cells of the superficial layer are on their basal side structurally identical with the underlying mesenchyme and some of their daughter cells become part of it.

Figs. 2 and 3.—Müllerian duct and surrounding tissues of a chick embryo of six days and three hours. Gomori's silver impregnation. Fig. 3 shows the beginning subdivision of the Müllerian primordium into the duct proper (M) and a tissue between it and the Wolffian duct (W) in which argyrophil fibers indicate the beginning transformation into mesenchyme (X). A more cranial section of the same duct (Fig. 3) shows this process in a farther advanced stage. The basal membrane of the original Müllerian primordium is dissolving (left side of figure), and the newly formed mesenchyme between the Wolffian and Müllerian ducts is now characterized by a typical argyrophil framework (X).

potencies to the lower portion of the peritoneal cavity. At the time when the primordia of the Müllerian ducts first appear, the urogenital ridges reach cranially to the level of the upper thoracic segments.

The possibility of origin of endometriosis from these tissues of the celomic walls accounts not only for the common locations of that anomaly, but also for one whose explanation appeared extremely difficult to previous investigators. This is endometriosis of the extremities.

In considering the embryologic basis of the endometriosis problem, we must first review certain aspects of the development of the celomic wall from which the Müllerian ducts eventually will originate. As has long been known, the celomic wall of early embryos does not consist of well-defined epithelium and connective tissue. The cells of the layer lining the celomic cavity have protoplasmic processes on their basal side, which are interwoven and structurally identical with those of the underlying mesenchymal cells (Fig. 1). Furthermore, many daughter cells of this superficial layer sink deeper into the tissue and become part of the mesenchyme. Thus, the celomic wall of the early embryo must be considered as one unit, comprising both the superficial and deep layers. Later, in human embryos during the fourth and fifth week, the superficial layer assumes all structural characteristics of a typical epithelium. However, as shown in a recent review,<sup>3</sup> this epithelium is still capable of cooperating with the adjacent mesenchyme in forming one common unit in which the two tissues cannot be distinguished. This happens particularly during early stages of organ formation from the celomic wall, such as in the initial phases of gonad and adrenal development. The fact that the limb buds develop from the celomic wall in a similar manner, will be discussed and evaluated below. The celomic lining may form mesenchyme long after its transformation into an epithelium. This happens particularly in the peritoneum, covering the Müllerian ducts, the so-called tubal ridge.<sup>3</sup> The readiness of the cells of the celomic wall to change from epithelial to mesenchymal arrangement, or vice versa, is also manifest in the organs developing from this tissue. This comprises the Müllerian ducts in addition to the gonads and adrenal cortex. These ducts, although originating as distinctly epithelial primordia from an epithelial portion of the celomic lining, give rise to typical embryonic connective tissue. This occurs to a considerable extent in chick and cat embryos where Müllerian cells near the caudal end of the growing duct change their properties and become part of the mesenchyme surrounding the duct itself<sup>3</sup> (Figs. 2 and 3). A similar condition was also found in human embryos, although probably not as extensively as in the chick.<sup>4</sup> It can thus be concluded that at least part of the nonepithelial tissues of the uterus are derived along with the epithelium from cells of the Müllerian ducts.

According to these considerations, the resultant tissues must be regarded as possible bearers of the potencies of endometrium formation. Nonepithelial cells of the uterine wall itself are closest related to the endometrial epithelium since part of them are derived from the Müllerian ducts at comparatively late embryonic stages, long after these ducts have acquired characteristic shape and differentiation. These cells must therefore be regarded as the possible source of those endometrioses of the uterus which are not continuous with the epithelium of the normal endometrium. In the second place we have to consider the mother tissue

and Filatow<sup>6</sup> describes early limb bud development in amphibians as occurring in a similar manner as briefly mentioned above in reference to early stages of gonad and adrenal development. Study of human and mammalian embryos reveals that here, too, the limb buds form from the parietal mesoderm at a time when the celomic lining (the later epithelium and mother tissue of the Müllerian ducts) still participates in the production of cells of that tissue. It can thus be seen that the mesenchyme of the limb bud is in its development closely related to the mother tissue of the uterine epithelium, both originating from the celomic wall. Figs. 4 to 6 may serve to illustrate the close relations of limb buds and urogenital ridges in early embryos. Fig. 4, taken from a cross section of a 5 mm. human embryo, shows the arm buds attached to the celomic wall in closest proximity of the cranial portion of the urogenital ridges, at a level very near the future site of the primordia of the Müllerian ducts. In Fig. 5, a similar picture is presented from the hind leg level of a 6.5 mm. rat embryo. Higher magnification (Fig. 6) reveals that even at this relatively late stage the celomic lining at the site of the leg primordium has not differentiated into an epithelium and may therefore still contribute to the tissue of the leg. We can thus include the extremities in our considerations concerned with the celomic walls. It is unnecessary to assume that all mesenchyme of the body may produce endometriosis, as was suggested by Biebl.<sup>2</sup>

In view of these close relations of limb primordia and urogenital ridges, one might almost wonder why we do not find many more cases of endometriosis of the extremities. However, we must remember that specialization of tissues proceeds during development, and the farther away an embryologically related tissue is in space or differentiation from the normal primordium, the less likely it will form germs resembling that primordium.

#### SUMMARY

Embryologic considerations show that endometriosis in all known locations may originate from the local tissues. The celomic walls, including epithelium and connective tissue, are in their development related to the Müllerian ducts and must therefore be regarded as possible bearers of the developmental potencies of endometrium formation. This also includes various structures arising from the celomic walls, among them the gonads and the extremities. The nonepithelial tissues of the uterus itself are in particular, closely related to the uterine epithelium, since part of their cells are given off by that epithelium (the Müllerian ducts) during embryonic life.

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It has long been known that the mesenchyme of the limb buds develops from the parietal mesoderm. Bardeen<sup>5</sup> describes this as follows: "In part it may come from the primitive body segments, but it seems probable that in the main it comes from the parietal layer of the unsegmented mesoblast." This parietal mesoderm is part of the celomic wall,



Figs. 4 to 6.—The close topographic relation of limb buds and urogenital ridges is illustrated by cross sections of the arm region of a 5 mm. human embryo (hematoxylin-eosin stain\*) (Fig. 4), and the hind leg region of a 6.5 mm. rat embryo (azan stain) (Fig. 5). Fig. 6 is a high-power view of the area marked in Fig. 5. The celomic lining adjoining the leg primordium (left side of figure) is still in its primitive condition comparable to Fig. 1, and can thus contribute to the tissue of the limb. A, Arm bud; H, hind leg primordium; L, liver; S, stomach; U, urogenital ridge; and W, Wolffian duct.

\*From the Embryological Collection of the Department of Anatomy, University of Illinois, Chicago. I am indebted to Dr. O. F. Kampmeier for his permission to use this specimen.

absorbed, leaving a deposit of crystals in the tissues to be absorbed slowly just as with implants. Laboratory experiments revealed that the estrus induced in castrate rodents with such a preparation persisted for a much longer time than with similar quantities of estrone in oil solution or even estrone suspended in oil.

We tested the therapeutic efficiency of aqueous suspension in a series of 44 menopausal patients. As a control we used 21 menopausal women to whom were given the same doses of estrone but suspended in oil instead of in water. The aqueous suspension in estrone proved to be superior to the oil suspension. In addition to the enhanced therapeutic efficiency, another advantage in using aqueous suspensions of estrone over oil solutions, is the freedom from possible sensitivity reaction to the oil.

All the patients received 5 mg. of estrone once a week for three weeks and some of them experienced relief for ten or more weeks after the last injection of aqueous estrone. It is doubtful that the estrone crystals were retained in the tissues for this length of time. It is more likely, as Salmon, Geist and Walter<sup>4</sup> have postulated for estrogen implants, that the slow uniform absorption of the estrogens allows for a physiologic readjustment to estrogen deprivation amounting at times to an actual curing of the patient.

#### SYNTHETIC ESTROGENS

In 1938 Dodds and his associates<sup>5</sup> synthesized diethylstilbestrol which possesses the properties of the natural estrogens. Stilbestrol is the mother substance from which diethylstilbestrol is derived. Stilbestrol has little estrogenic activity, whereas diethylstilbestrol (generally referred to as stilbestrol in the literature) has great estrogenic effect. The advantages of the synthetic estrogens are the great effectiveness of oral administration and their low cost. A disadvantage is that a fairly large proportion of the women who take diethylstilbestrol, experience disagreeable symptoms, chiefly nausea, vomiting, epigastric pain, headache, and dizziness. Generally the larger the dose taken the greater the likelihood of distress, because in most cases reducing the dosage eliminates the aftereffects. Thus far it has not been proved in human beings that diethylstilbestrol produces damage to any organs even when huge doses are administered. Notwithstanding the absence of proved injury, attempts have been made to synthesize estrogens which will be just as effective as diethylstilbestrol but will produce fewer disturbances. During the last few years, Dr. Freed and I have investigated not only diethylstilbestrol, but also hexestrol and a product known as 118-B.\*

In most instances the claims for the relative therapeutic effectiveness of estrogens have been based on their activity as determined in laboratory animals, principally the rat and mouse. The assumption that data

\*The diethylstilbestrol and the hexestrol were supplied by the Abbott Laboratories and the 118-B was prepared by Schieffelin & Co.

## THE USE AND POTENCY OF SYNTHETIC ESTROGENS\*

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NOTWITHSTANDING the vast and ever-increasing literature on endocrinology, I am less enthusiastic now about the value of general endocrine therapy in gynecology than I was a few years ago. However, this does not apply to the estrogens. Today there is a more widespread use of the estrogens than formerly, and this appears to be warranted. The estrogens have a large field of usefulness in gynecology and a limited applicability in obstetrics. All investigators agree that estrogens readily suppress undesired lactation. These hormones are occasionally of benefit for the induction of labor, particularly in cases of missed labor, if used in very large doses and especially if combined with posterior pituitary extract. Likewise, the estrogens are sometimes helpful in cases of uterine atony during labor. White and Hunt<sup>1</sup> have found the estrogens most helpful in the treatment of diabetes in pregnancy and Van S. Smith and Smith<sup>2</sup> observed encouraging results with estrogens (combined with progesterone) in the toxemias of pregnancy.

In gynecology the prime indication for the use of estrogens is to overcome the distressing symptoms of the menopause. However, these hormones are also of distinct benefit in cases of gonorrheal vulvovaginitis, vaginal hypoplasia, senile vaginitis, menometrorrhagia and some cases of dysmenorrhea. The estrogens have also been used to overcome other abnormal conditions such as amenorrhea, hypoplasia of the uterus, and underdevelopment of the breasts, but in my opinion changes following such therapy are only temporary. The estrogens may be administered by mouth, sublingually, by hypodermic, by vagina, by rectum, by local application in an ointment, and by subcutaneous implantation in the form of crystals or pellets. For most indications, the subcutaneous route yields the best results but for some conditions such as gonorrheal vulvovaginitis and senile vaginitis, the local application of the hormone is preferable. Where prolonged action is desired, the subcutaneous implantation of pellets and crystals of estrogen is most helpful. However, because of the hesitancy of most physicians to resort to subcutaneous implantation, my associate Dr. S. C. Freed and I utilized the principle of implantation of crystalline estrogens in a form which does not sacrifice the convenience or practicability of simple injections. We utilized a suspension of estrone crystals in an aqueous medium on the assumption that, after injection into the tissues, the aqueous medium is rapidly

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\*Read at a meeting of the Obstetrical Society of Boston, February 17, 1942.



at least two distinct hot flushes daily together with other symptoms commonly found in the menopause, such as nervousness, irritability, and emotional instability. The psychic factors associated with any form of therapy involving subjective sensations were reduced to a minimum by eliminating any therapeutic suggestions, such as a promise of beneficial results or leading questions concerning the therapeutic responses. In addition, the subjective changes of all the patients were evaluated by us alone in as constant a manner as possible, thus eliminating differences in interpretation of results which are prone to develop where a number of clinicians are treating the same group of patients. Furthermore, the estrogens were administered in several dose levels in the manner which is used for assaying estrogens in laboratory animals. Following are the data of three synthetic estrogens, diethylstilbestrol, hexestrol and 118-B, assayed in this manner.

#### METHODS AND RESULTS

The procedure carried out in the experiments was as follows: At various intervals, patients were given different levels of one of the three synthetic estrogens for oral use. For example, some women were given 1 mg., 2.5 mg., and 5 mg. daily of hexestrol, others received 0.5 mg. and 1 mg. of diethylstilbestrol and still others were given 1 mg., 2.5 mg., and 5 mg. of 118-B. Therapy was usually started by administering the highest level of the estrogen. After three weeks of treatment, the therapeutic response was evaluated and recorded in the following terms: "negative," "slight," "good," and "excellent." In the evaluation of the therapeutic response, the disappearance of the hot flushes was used as the most important criterion of relief. The other menopausal symptoms, such as nervousness, perspiration, irritability, etc., were also considered in this evaluation. After the first period of treatment, the dosage was dropped to the next lower level and maintained in this manner for three or more weeks. After the patient's response to the new dosage was evaluated, the dose in the case of hexestrol and 118-B was dropped to the third level and this was maintained for at least three weeks after which another evaluation was made. Following this, the type of estrogen administered was changed. Some women did not complete the entire course of assays due to refusal, because of unpleasant symptoms which arose, lack of cooperation, and other reasons. However, 82 women were given all three synthetic estrogens, 118 women were given diethylstilbestrol and hexestrol, and 44 women were given only the three different doses of hexestrol. With the use of the technique we employed, there is no need for control with either untreated patients or patients who receive placebos, inasmuch as each dosage level controls the next. The psychic factor of administering some form of medication is thus reduced.

Tables I to III show the therapeutic results of the assays of the three synthetic estrogens and also the incidence of unpleasant symptoms.

#### THERAPEUTIC RESPONSE OF MENOPAUSAL PATIENTS FOLLOWING ORAL ADMINISTRATION OF DIETHYLSTILBESTROL, HEXESTROL AND 118-B

Table I indicates that of the 53 women who took 0.5 mg. diethylstilbestrol daily, 9 derived no benefit, 17 had slight improvement, 18 were

so obtained can be accepted for the human being has resulted in considerable confusion in the standardization of estrogen therapy. In the first place, results obtained from assays differ widely, as indicated by the fact that the rat unit of estrone as determined in different laboratories, varies as much as several thousand per cent when compared to a weighed amount of crystalline material. The same applies for assays in the mouse. In a compilation of data on the subject, Freed<sup>6</sup> illustrated the inconsistencies in animal assays and came to the conclusion that any statement regarding the relative therapeutic activity of estrogens on the basis of animal assays is liable to considerable error. For this reason I believe that at present the only satisfactory test object for the therapeutic efficiency of the estrogens is the human being.

There are a number of ways of assaying the activity of estrogens in the human being. Some investigators utilize the changes in the vaginal mucosa of menopausal women following estrogen administration as an index of estrogen activity, in a manner similar to that of the castrate rodent. There are objections to this index. In the first place, it requires considerable experience to read properly and interpret vaginal smears, and second, the reading is subject to much experimental error. Furthermore, since we know that untreated menopausal women have varying degrees of proliferation of the vaginal mucosa, this cannot be an entirely satisfactory means of assay. Still further, there is no evidence that the vaginal mucosa of a group of menopausal women will respond to a definite amount of estrogen with the same degree of uniformity.

An attempt has been made to use the endometrium as a means of assaying estrogens administered during the menopause. This procedure is distinctly more cumbersome than the use of vaginal smears and is open to even more criticism than the latter. Untreated menopausal women by no means uniformly present an atrophic endometrium. Many show not only endometrial proliferation but actual hyperplasia. Hence, endometrial changes cannot be used as criteria for estrogen activity.

In our investigation we have selected as the end point in the assay of estrogens in human beings, the subjective response of menopausal patients. It is acknowledged that the evaluation of such a response may be obscured by numerous uncontrolled factors. Nevertheless, this method has been selected for the assay for a number of reasons, not the least of which is the fact that the chief purpose in administering estrogens is to relieve the menopausal patient of her subjective symptoms. Such an assay requires no special technique and a large number of patients may be included in a study with little difficulty. In order to eliminate as many distracting factors as possible from this study, we established certain criteria. Only those patients were selected who complained of moderate or severe menopausal symptoms. Those who had complaints which were of doubtful origin or possibly might be confused with psychic changes due to environmental or social complications, were not included in the group tested. The patients treated were limited to those having

TABLE III. 118-B

| 1 MG. DAILY     |           |                | 2 MG. DAILY     |           |                | 5 MG. DAILY     |           |                |
|-----------------|-----------|----------------|-----------------|-----------|----------------|-----------------|-----------|----------------|
| NO. OF PATIENTS | RESULT    | TOXIC REACTION | NO. OF PATIENTS | RESULT    | TOXIC REACTION | NO. OF PATIENTS | RESULT    | TOXIC REACTION |
| 2               | Negative  |                | 5               | Negative  |                | 3               | Negative  |                |
| 5               | Slight    |                | 9               | Slight    |                | 1               | Slight    |                |
| 14              | Good      |                | 16              | Good      |                | 7               | Good      |                |
| 4               | Excellent |                | 9               | Excellent |                | 7               | Excellent |                |
| 25              |           | 0              | 39              |           | 1<br>2.6%      | 18              |           | 2<br>11.1%     |

ment, 7 were satisfactorily relieved, and 7 had complete relief. Of these 18 women, 2 (11.1 per cent) experienced disagreeable symptoms.

It will be noted that a larger number of patients failed to respond to 5 mg. hexestrol than to 2.5 mg. of this substance. This apparent paradox is due to the fact that the women were first given the largest doses. Those who failed to respond at all were not given the 2.5 mg. dose. The 7 women who failed to respond to the 2.5 mg. dose had received benefit from the 5 mg. dose.

It is apparent from the data in the tables that a satisfactory daily therapeutic dose of diethylstilbestrol is 1 mg., of hexestrol 2.5 to 5 mg., and of 118-B, 1 to 2 mg. The minimal effective doses are 0.5 mg. diethylstilbestrol, 2.5 mg. hexestrol, and 1 mg. 118-B.

Of 46 women questioned concerning the relative merits of diethylstilbestrol and hexestrol the response was as follows:

28 found 2.5 mg. hexestrol daily equal to 0.5 mg. diethylstilbestrol  
 14 found 2.5 mg. hexestrol daily better than 0.5 mg. diethylstilbestrol  
 4 found 2.5 mg. hexestrol daily less effective than 0.5 mg. diethylstilbestrol

Likewise, among 48 women the following observations were made:  
 34 found 5 mg. hexestrol daily equal to 1 mg. diethylstilbestrol  
 6 found 5 mg. hexestrol daily better than 1 mg. diethylstilbestrol  
 8 found 5 mg. hexestrol daily less effective than 1 mg. diethylstilbestrol

The incidence of toxic manifestations which is associated with the ingestion of the synthetic estrogens is an important matter, particularly because apparently this is the only drawback to the use of these estrogens. The tables indicate that the larger the dose of these estrogens, the greater the incidence of toxicity. Hexestrol is significantly less toxic than diethylstilbestrol, although the incidence of disagreeable symptoms from hexestrol is appreciable. Likewise, 118-B is definitely less toxic than either of the other two, and it is probably no more toxic than the natural estrogens. However, more data are necessary before this point can be determined definitely.

The results of this study are at variance with those of Bishop and his associates.<sup>7</sup> These investigators reported that hexestrol and diethylstilbestrol are of equal potency, but our study shows that hexestrol is only about one-fifth as effective as diethylstilbestrol. Furthermore, Bishop maintains that hexestrol is relatively free of untoward reactions. While we have found that hexestrol is definitely less toxic than diethylstilbestrol, it is by no means free from unpleasant sequelae.

TABLE I. DIETHYLSTILBESTROL

| 0.5 MG. DAILY   |           |                | 1 MG. DAILY     |           |                |
|-----------------|-----------|----------------|-----------------|-----------|----------------|
| NO. OF PATIENTS | RESULT    | TOXIC REACTION | NO. OF PATIENTS | RESULT    | TOXIC REACTION |
| 9               | Negative  |                | 5               | Negative  |                |
| 17              | Slight    |                | 10              | Slight    |                |
| 18              | Good      |                | 27              | Good      |                |
| 9               | Excellent |                | 23              | Excellent |                |
| 53              |           | 5<br>9.4%      | 65              |           | 18<br>27.7%    |

satisfactorily relieved and 9 had complete relief from all symptoms. In this group of 53 women, 5 (9.4 per cent) experienced unpleasant reactions, such as nausea, headache, and dizziness. Of the 65 women who took 1 mg. diethylstilbestrol daily, 5 derived no benefit, 10 had slight improvement, 27 were satisfactorily relieved and 23 had complete relief. In this group of 65 women, however, 18 (27.7 per cent) experienced unpleasant symptoms. This agrees with the almost universal opinion that the larger the dose of diethylstilbestrol taken, the greater the frequency of disagreeable symptoms.

TABLE II. HEXESTROL

| 1 MG. DAILY     |          |                | 2.5 MG. DAILY   |           |                | 5 MG. DAILY     |           |                |
|-----------------|----------|----------------|-----------------|-----------|----------------|-----------------|-----------|----------------|
| NO. OF PATIENTS | RESULT   | TOXIC REACTION | NO. OF PATIENTS | RESULT    | TOXIC REACTION | NO. OF PATIENTS | RESULT    | TOXIC REACTION |
| 21              | Negative |                | 7               | Negative  |                | 15              | Negative  |                |
| 10              | Slight   |                | 13              | Slight    |                | 5               | Slight    |                |
| 6               | Good     |                | 29              | Good      |                | 22              | Good      |                |
|                 |          |                | 11              | Excellent |                | 23              | Excellent |                |
| 37              |          | 0              | 60              |           | 2<br>3.3%      | 65              |           | 9<br>14%       |

Table II shows that of the 37 women who took 1 mg. hexestrol daily, 21 derived no benefit, 10 had slight improvement, and 6 were satisfactorily relieved. No patients in this group experienced unpleasant symptoms. Of the 60 women who took 2.5 mg. hexestrol daily, 7 derived no benefit, 13 had slight improvement, 29 were satisfactorily relieved, and 11 had complete relief. In this group of 60 women, 2 (3.3 per cent) experienced unpleasant symptoms. Of the 65 women who took 5 mg. hexestrol daily, 15 derived no benefit, 5 had slight improvement, 22 were satisfactorily relieved and 23 had complete relief. Of these 65 women, 9 (14 per cent) experienced disagreeable side effects. As with diethylstilbestrol, the larger dose produced a greatly increased incidence of nausea, headaches, and dizziness.

Table III shows that of the 25 women who took 1 mg. of 118-B daily, 2 derived no benefit, 5 had slight improvement, 14 were satisfactorily relieved, and 4 were completely relieved. None of these 25 women experienced unpleasant reactions. Of the 39 women who took 2 mg. of 118-B daily, 5 derived no benefit, 9 had slight improvement, 16 were satisfactorily relieved, and 9 had complete relief. Only 1 of these 39 women (2.6 per cent) had nausea and dizziness. Of the 18 women who took 5 mg. of 118-B daily, 3 derived no benefit, 1 had slight improve-

family and past history were irrelevant. Examination revealed an eight months' gestation. Clumps of pus cells were found in the urine. The day after admission pain developed in both lumbar areas associated with chills and fever of  $100.4^{\circ}$  F. The pyrexia and discomfort continued intermittently for twelve days. Urine cultures grew Flexner dysenteriae on seven different occasions between April 12 and June 17. During the same interval, six stool cultures were negative for the same organisms.

After administering 18 Gm. of sulfanilacetylmid within three and one-half days, April 14 to 17, there was no further temperature elevation. However, the urine cultures remained positive for bacilli Flexner. On June 1, 1940, the patient delivered a normal, mature, female infant who was found to have Flexner dysenteriae in the urine after the first week of life. On Nov. 7, 1940, and Sept. 10, 1941, urine cultures from the mother showed no pathogenic organisms. The baby was not re-examined, but according to the mother there were no gastrointestinal or urinary disturbances during the first fifteen months of life.

CASE 2.—(38-14983.) A white, 32-year-old, para ii was admitted April 25, 1940, in labor at term. The past and family history were not unusual except that the patient had acquired syphilis in 1927. Subsequently adequate antisiphilitic therapy was given. The catheterized urine showed a trace of albumin and many clumps of pus cells.

After a five-hour labor, a normal, female child, weighing 2,705 Gm., was born. On the seventh post-partum day, the mother developed a one-day fever with a temperature of  $101.4^{\circ}$  F., and with urinary frequency and dysuria. The urine revealed pus and cultures were positive for Flexner dysenteriae. Symptoms disappeared after two days' bed rest and administration of four liters of fluids daily. The mother left the hospital on the ninth post-partum day before further studies could be made.

CASE 3.—(40-5700.) A 27-year-old, white, para i, was admitted April 25, 1940. The past and family history were normal. About March 25, two months after the last menstrual period, the patient began to have severe shaking chills, pain in both flanks radiating to the costovertebral angles, urinary frequency, dysuria, and cloudy urine. These symptoms were associated with hyperemesis gravidarum. The uterus, the size of a four months' gestation, was larger than the history would indicate. There was fever of  $101.5^{\circ}$  F. The white count was 6600, hemoglobin 11 Gm. (Haden-Hausser), and blood agglutination tests for Malta fever, typhoid, paratyphoid A and B, Rocky Mountain spotted fever, tularemia, and dysentery were negative. The urine contained 22 pus cells per high power field with one-plus albumin, but no sugar or blood. Cultures of the urine grew Flexner bacilli. Intravenous and retrograde pyelograms were normal except for mild right hydronephrosis.

Treatment consisted in administration of 3,500 c.c. of fluids daily and bed rest. Within four days, the symptoms disappeared and the patient went home. Approximately one month later the family physician reported that the patient had a recrudescence of the urinary infection and made the statement that the gastrointestinal tract was free of infection. Symptoms were alleviated by giving neoprontosil, grain xl, daily for one week. The antepartum and puerperal course then continued uneventfully.

## SUMMARY

Three synthetic estrogens, diethylstilbestrol, hexestrol, and 118-B were tested for their therapeutic efficiency by assay in humans. The subjective response of menopausal patients was used as the end point in this assay. The usual uncontrolled factors encountered in such a study were largely eliminated by using multiple dosage levels of the estrogens as well as other precautions. The results indicate that all three synthetic estrogens are highly effective in relieving the distressing symptoms of the menopause if proper dosages are used. A satisfactory daily therapeutic dose of diethylstilbestrol is 1 mg., of hexestrol, 2.5 to 5 mg., and of 118-B, 1 to 2 mg. The larger the dose of synthetic estrogen used, the greater the likelihood of untoward reactions. Hexestrol is definitely less toxic than diethylstilbestrol, and 118-B is far less toxic than either diethylstilbestrol or hexestrol.

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## URINARY INFECTION IN PREGNANCY DUE TO FLEXNER DYSENTERIAE

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**S**HIGELLA *paradysenteriae* (flexneri) seldom has been described as the causative organism in pyelitis and/or cystitis of pregnancy. For this reason four cases are reported, with four others described in the literature. The communication emphasizes that urinary infections of this nature have usually not been preceded by clinical evidence of gastrointestinal disease, and that confusion may arise in proving the identity of the Flexner organism bacteriologically.

## CASE REPORTS

CASE 1.—(38-1879.) A 23-year-old para ii was admitted April 10, 1940, in the eighth lunar month of pregnancy, with a history of chilliness, fever, and costovertebral angle tenderness for several days. The

TABLE I. DATA ON EIGHT RECORDED CASES OF URINARY TRACT INFECTION IN PREGNANCY DUE TO FLEXNER DYSENTERIAE

| AUTHOR                          | NO. OF CASES | AGE OF PATIENT  | DURATION OF PREGNANCY IN MONTHS | URINE CULTURE (FLEXNER)                 | STOOL CULTURE                           | BLOOD AGGLUTINATION FOR DYSENTERY | CLASSICAL DIAGNOSIS | THERAPY   |
|---------------------------------|--------------|-----------------|---------------------------------|---|---|-----------------------------------|---------------------|---|
| Calalb and Jonesco <sup>1</sup> | 1            | ? Primi-gravida | 8                               | Positive                                | One positive                            | Negative                          | Pyelo-nephritis     | Given antvaccine for six days                                   |
| Cheatham <sup>2</sup>           | 1            | 25              | 7                               | Positive*                               | Positive                                | Positive 1/640                    | Pyelo-nephritis     | Bacteriophage introduced into kidney pelvis and intramuscularly |
| Stewart <sup>3</sup>            | 1            | 20              | 2 (recurrent attacks)           | Positive                                | Positive                                | Positive 1/640                    | Pyelitis            | Ureteral catheterization and interruption                       |
| Van Ravenswaay <sup>6</sup>     | 1            | 27              | 5                               | Positive*                               | Positive                                | Negative                          | Pyelitis            | Mandelic acid and sulfanilamide                                 |
| Diddle and McKee                | 1            | 27              | 4 (recurrent attacks)           | Positive (with few <i>B. coli</i> once) | Negative                                | Negative                          | Pyelitis            | Neoprontosil  |
|                                 | 1            | 23              | 9                               | Positive                                | Positive once (contaminated with urine) | Negative                          | Pyelitis            | Sulfanilacetylmid   |
|                                 | 1            | 32              | Seventh post-partum day         | Positive* (Baby also had positive)      | Negative (Baby's stool negative)        | Not done                          | Cystitis            | No specific therapy   |
|                                 | 1            | 14              | 7.5                             | Positive                                | Negative                                | Not done                          | Cystitis            | No specific therapy   |

\*Reported negative three weeks to three months later.

CASE 4.—(42-2405.) A 14-year-old primigravida was admitted March 10, 1942. The uterus was the size of a thirty weeks' gestation, and catheterized urine specimens repeatedly showed many clumps of pus. Cultures were positive for Flexner bacilli. The ante-partum course remained normal even though no specific therapy was instituted. Record of the post-partum course was not available.

#### BACTERIOLOGY

*Shigella paradysenteriae* (*Bacterium flexneri*) was isolated in pure culture from the urine of four patients. There were 19 urine and 10 stool examinations. The urine samples were inoculated into dextrose meat infusion broth and on eosin-methylene-blue and blood agar plates; the latter were placed under 10 per cent carbon dioxide. Nonlactose fermenting colonies were transferred to Russell's double sugar agar slants, which were later used to inoculate dextrose, mannite, maltose, lactose, xylose, and sucrose fermentation tubes. Tryptophane broth was also inoculated and likewise agar slants, the latter for the purpose of obtaining agglutinogen.

The stool specimens were cultured in selenite F enriched broth and on desoxycholate and eosin-methylene-blue plates. If, after twenty-four hours, nonlactose fermentors were not found on the plates, new plates were inoculated from the selenite broth. Nonlactose fermenting colonies were treated as described previously.

The organisms in each case were gram-negative, indole producing, non-motile rods that fermented dextrose, mannite, maltose, and xylose, but failed to ferment lactose and sucrose. The lactose fermentation tubes were held two weeks before being discarded as negative.

In all cases the identification was confirmed by agglutination tests. Twenty-four-hour cultures on meat infusion agar slants were suspended in 0.9 per cent saline and routine agglutination tests made. The isolated organisms were then set up against the following antisera: polyvalent dysentery, Flexner, Hiss, and Sonne dysentery, typhoid, and paratyphoid A and B. Agglutination titers are recorded in Table II. Agglutination studies using the patient's serum against isolated strains of *Shigella paradysenteriae* were not done.

#### DISCUSSION

Perusal of the literature disclosed four additional cases of urinary infection in pregnancy due to bacillary dysentery, Flexner. Between Jan. 1, 1939, and March 1, 1942, there have been four cases among 5,504 obstetric admissions to this Hospital, or an incidence among urinary infections of 1 to 18.

Table I shows that 7 of the 8 patients had their initial symptoms ante-partum and one post partum. Clinically 2 had pyelonephritis, 2 cystitis, and 4 pyelitis. Recrudescences occurred in 2 patients. In one instance the pregnancy was interrupted because there was no response to ureteral catheterization (Stewart, 1938). Treatment in the other seven cases included sulfonamides, 3; antivaccine, 1; bacteriophage, 1; and no



a high titer is not to be anticipated and there may be a complete absence of demonstrable agglutinins. Checking the organism against antisera for typhoid, paratyphoid A and B helps to eliminate the possibility of an atypical typhoid or paratyphoid organism. Holding the lactose medium for two weeks aids in ruling out the paracolon group which at times may mimic typhoid, paratyphoid, or dysentery organisms. It is probable that urinary tract infection in pregnancy due to the Flexner organism is not as rare as the literature suggests, but failure to ascertain its presence is due either to confusing it with the paracolon group or to inadequate bacteriologic study.

#### SUMMARY AND CONCLUSIONS

Analysis of 8 cases of urinary tract infection in pregnancy due to *Shigella paradysenteriae* (*Bacterium flexneri*) revealed that the clinical symptoms produced might be severe or of only minor importance. Since treatment varied considerably, no comment on therapy is warranted, except to say that this type of infection seemed to respond to the usual measures employed for cystitis or pyelitis. An incidence of one in 18 obstetric urinary tract infections attributed to the Flexner organism suggests that this type of infection is more common than formerly believed.

Previous history of gastrointestinal disease was usually not obtained. The organism may be confused with the paracolon group. Differentiation and identification require thorough cultural and serologic study.

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Eagle, Harry, and Hogan, Ralph B.: The Intravenous Drip and Other Intensive Methods for the Treatment of Early Syphilis, Science 95: 360, 1942.

The authors used over 2,000 syphilitic rabbits, treated with mapharsen, on the following twelve experimental schedules:

- Intravenous drip (5 to 6 hours daily) for 1, 2, and 4 days.
- Multiple injections each day for 1, 2, and 4 days.
- Single daily injections for 1, 4, and 12 days.
- Injections every other day (3 times weekly) for 4 and 8 weeks.
- Weekly injections for 6 weeks.

They arrive at the conclusion that the margin of safety and the amplitude of tolerated dose over minimum curative dose could be increased by prolongation of treatment. Furthermore, the authors are of the opinion that their assumptions can be applied to human beings. A safe compromise can be worked out between the unduly prolonged eighteen-month schedule, and the dangerous 5-day program. Twelve clinics are now submitting these results to clinical trial.

L. M. HELLMAN.

specific measures except increasing the fluid intake, 2. Five women had bacteriologic evidence of gastrointestinal infection. However, two of the five had only one positive stool culture. It was known that the specimen of one patient had been contaminated with urine.

Seven other cases of urinary infection in nonpregnant females and males (Forester, 1918; Neter, 1937) were gathered from the literature. The authors have seen three others (one baby, one woman, one man). Seven of the 10 were girls, 1 a nonpregnant woman, and 2, men. The girls had pyuria, either with or without symptoms of cystitis or pyelitis, while the woman contracted pyelonephritis during the course of a gastrointestinal infection, and the men had pyelitis.

The preponderance of this type of infection in females would suggest that ascending infection through the bladder is more easily acquired, probably because the urethral orifice is not as well shielded anatomically as in males.

TABLE II. RESULTS OF AGGLUTINATION TITERS FOR POLYVALENT DYSENTERY AND FLEXNER DYSENTERIAE ANTISERA

| CASE                    | SPECIMEN | NUMBER OF SPECIMENS | POLYVALENT DYSENTERY ANTISERUM*  | FLEXNER ANTISERUM†               | REMARKS                                   |
|-------------------------|----------|---------------------|----------------------------------|----------------------------------|---|
| 38-1879                 | Urine    | 7                   | 1:80                             | 1:160                            | Urine cultures negative five months later |
|                         | Stool    | 6                   | No dysentery organisms isolated  |                                  |   |
| Newborn baby of 38-1879 | Urine    | 3                   | 1:320                            | 1:640                            | No later cultures or agglutinin studies   |
|                         | Stool    | 2                   | No dysentery organisms isolated  |                                  |   |
| 38-14983                | Urine    | 2                   | 1:160                            | 1:320                            | Subsequent studies not done               |
| 40-5700                 | Urine    | 3                   | Positive, but titer not recorded | Positive, but titer not recorded | Recrudescence of infection in pregnancy   |
|                         | Stool    | 1                   | No dysentery organisms isolated  | No dysentery organisms isolated  |   |
| 42-2405                 | Urine    | 4                   | 1:320                            | 1:640                            | Pyuria                                    |
|                         | Stool    | 1                   | No dysentery organisms isolated  | No dysentery organisms isolated  |   |

\*An original titer of 1:4,000 against homologous strain.

†An original titer of 1:1,280 against homologous strain.

From the bacteriologist's point of view one must be prepared to find dysentery organisms in locations other than the gastrointestinal tract. *Shigella paradysenteriae* (flexneri) were found in this institution from a cutaneous abscess (1) and a cervix (1). In each case stool and urine cultures were negative and no agglutinins were demonstrable. Also, there was no other pathologic process from which the organism might have invaded the infected area. In addition to the cultural and serologic studies described, the patient's blood should be tested for agglutination against known strains of dysentery organisms. In early cases, however,

hemorrhage after its removal. The nidation site and the pelvic organs were subjected to careful examination following autopsy. A committee of the London Obstetrical Society studied the findings, and, while admitting the possibility that the site of the pregnancy might have resulted from secondary implantation after early extrusion of the ovum from a primary fimbrial nidation, came to the conclusion that the case represented a true primary peritoneal pregnancy. Wittauer<sup>14</sup> (1903) next reported a patient, in whom the tubes and ovaries were found to be normal, the omentum containing a small blood clot in which chorionic villi were found. These findings might also have been produced by the early extrusion of a fimbrial tubal pregnancy with secondary implantation in the omentum. Hirst and Knipe<sup>15</sup> (1908) report what appears to be an undoubted instance, the ovum being about six weeks of age and implanted in the back of the left broad ligament above and to the outer side of the uterosacral ligament. The posterior leaf of the broad ligament formed the reflexa covering the maternal blood space. The tubes and ovaries appeared normal. Hammacher<sup>16</sup> (1910) reported an instance in which it was thought that the ovum was implanted on the external peritoneal aspect of the right tube. Maxwell, Eastman and Smetana<sup>17</sup> (1927) reported a similar case in which the ovum was thought to be implanted on the external surface of an apparently completely occluded left tube. In both the latter instances, while the microscopic sections seem convincing, the very location of the pregnancy gives rise to some doubt as to whether the ovum did not enter through the tubal mucosa.

These cases by no means represent a complete survey of the literature but illustrate the manner in which the possibility of true peritoneal implantation may be questioned. The case reported by Hirst and Knipe<sup>15</sup> (1908) appears to be least open to doubt. Because the following case appears to lend strength to the possibility that primary peritoneal nidation may take place, it was thought to be worthy of report.

#### CASE REPORT

Mrs. S. I., aged 27 years, para i, gravida ii, was admitted on Oct. 14, 1940, to the Gynecological Service, Bellevue Hospital, with a chief complaint of pain in the lower abdomen, radiating upward to the chest. This had begun suddenly at noon of the same day following violent sexual intercourse. Nausea and vomiting had occurred five times since the onset of pain. Her last menses had occurred on Sept. 14, 1940, and her following period was about two weeks overdue.

General examination showed a young woman who appeared in mild shock. Her blood pressure was 82/68, pulse, weak with a rate of 114, and temperature, 97° F. General physical examination revealed the following positive findings. The abdomen showed moderate soft distention with generalized tenderness. No rigidity was present. Pelvic examination showed the cervix to be posterior, closed, and firm. It was normal in appearance and showed no discharge. The corpus uteri was anterior, not enlarged, and nothing abnormal could be made out in either adnexal region except for moderate tenderness. The white blood count showed 13,300 with 83 per cent polymorphonuclear leucocytes. The hemoglobin was found to be 92 per cent (Dare). Urine examination showed negative findings.

## PRIMARY PERITONEAL PREGNANCY

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IN THE vast majority of instances, extrauterine pregnancy results from the nidation of a fertilized ovum in some portion of the mucosal lining of the Fallopian tube. The selection of this point of nidation appears to rest on a delay of eight to nine days in the transit of such an ovum to the uterine cavity.<sup>1, 2</sup> The factors producing delay may be obvious, as in chronic salpingitis, or obscure. Much more rarely ectopic gestation results from a failure of the ruptured Graffian follicle to expel the mature ovum. Subsequent fertilization within the follicular space gives rise to one of the two forms of primary ovarian pregnancy.<sup>3</sup> The present knowledge of the active part played by the tube in securing the freshly expelled ovum,<sup>4, 5</sup> together with the fact that about eight to nine days elapse before the fertilized ovum becomes capable of nidation,<sup>1, 2</sup> explains quite obviously why primary extrauterine pregnancies are found most commonly in these two locations. These factors would seem to play a much greater part than the hypothesis which has been put forward that nidation can take place only in Müllerian tissue.<sup>6</sup>

Should the ovum be expelled from the follicle, become fertilized, and develop over a period of eight to nine days<sup>1, 2</sup> without being captured by the fimbriated extremity of the tube, it seems most likely to the author that nidation will take place in any tissue, regardless of its origin, with which the blastocyst is in contact. With the exception of the germinal epithelium of the ovary, such tissue must be either visceral or parietal peritoneum. Such a pregnancy must be termed a primary peritoneal pregnancy.

The criteria upon which the proof of such a pregnancy must rest are: (1) that both tubes and ovaries are normal with no evidence of recent or remote injury, (2) the absence of any evidence of a uteroperitoneal fistula, and (3) the presence of a pregnancy related exclusively to the peritoneal surface and young enough to eliminate the possibility of secondary implantation following a primary nidation in the tube. Some authorities<sup>7-9</sup> state that primary abdominal pregnancies are rare, while others,<sup>10, 11</sup> most recently Novak,<sup>12</sup> deny the possibility of this type of extrauterine gestation.

In reviewing some of the more widely quoted instances in the literature, the first case reported appears to be that of Gallabin<sup>13</sup> (1896). His patient showed a ten weeks' ovum in the cul-de-sac. She died from

the uterus showed a defect. Beneath this the myometrium contained a rounded cavity filled with blood clot, the peripheral portions of which contain chorionic villi covered with an active well-preserved double layer of epithelium. The central stroma of the villi was made up of edematous embryonal connective tissue. Blood vessels were only occasionally noted. Some of the villi were actively invading the myometrium. No decidual reaction was noted about the implantation site. Only the peripheral villi were present, no evidence being found of a central vesicle. It is believed that this must have been extruded at the time of rupture. In all the sections the mucous membrane of the interstitial tube was intact, as well as the muscularis. At no point did the pregnancy approach the tubal lumen to any closer degree than can

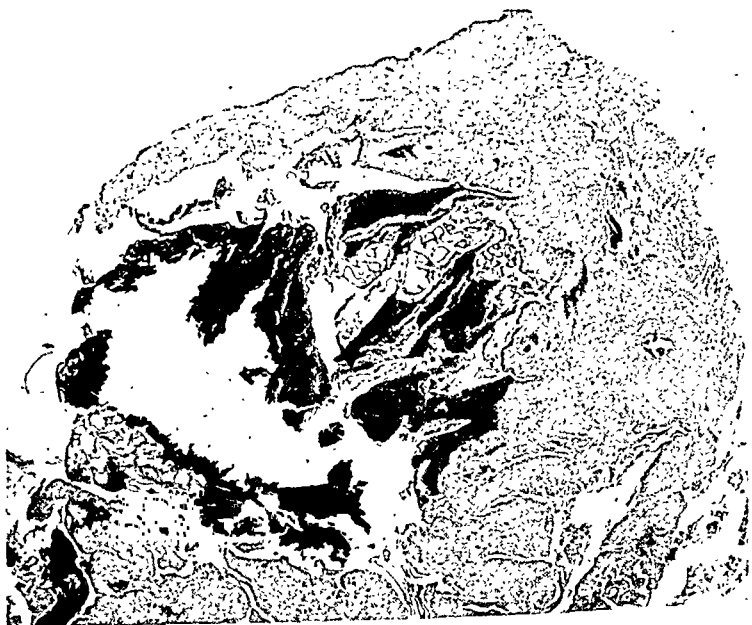


Fig. 3.—Low power photomicrograph showing maternal blood space with rupture through serosa of uterus, and separated from tubal lumen by myometrium, tubal muscle, and mucosa. This space contains blood clot and well-preserved, young chorionic villi, but the central vesicle is absent, apparently having been extruded at the time of rupture.

be seen in the photomicrograph (Fig. 3). From the history, the size of the nidation site, and the appearance of the villi, it is believed that the ovum could not have exceeded four weeks in age. Its early age makes it most improbable that the site of nidation could have been secondary.

#### COMMENT

These findings give rise to the question as to how this pregnancy occurred in the location described. If it is an interstitial tubal pregnancy the embedding ovum must have traversed the tubal mucosa, the tubal muscle, and a considerable area of myometrium to reach this location. Furthermore it must have accomplished this without leaving a trace of its passage. This is impossible to believe. The only other approach to this location is through primary nidation on the peritoneal surface of the uterus. It is unfortunate that the pregnancy is so closely

Because of the history, the diagnosis of an internal injury, possibly involving the bladder, was entertained, but, by the following morning, increasing evidence of intraperitoneal hemorrhage was present. A laparotomy was performed with a preoperative diagnosis of extrauterine pregnancy. On opening the abdomen through a lower abdominal mid-line incision, the peritoneal cavity was found to be filled with fluid and clotted blood. Both tubes, ovaries, and broad ligaments appeared to be perfectly normal. The uterus was in normal position, not enlarged. On the posterior aspect, about  $1\frac{1}{2}$  cm. medial to the insertion of the left tube was a small round slightly elevated bluish area about 7 to 8 mm. in diameter. In the center of this was a small ragged opening about 1 mm. in diameter from which active bleeding was taking place (Fig. 1). The left horn of the uterus containing the entire involved area was removed, the uterine wound being closed by sutures. The remainder of

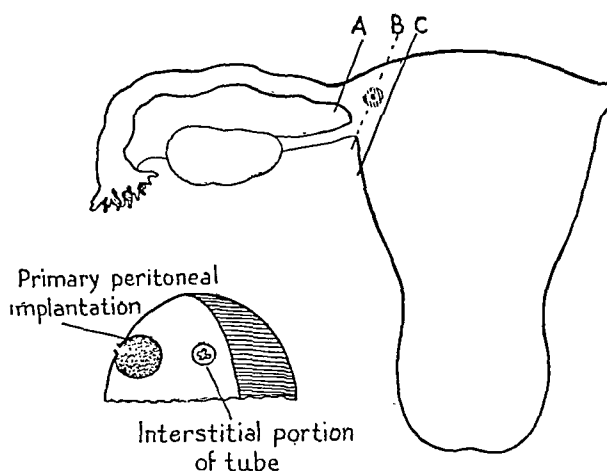


Fig. 2

Fig. 1

Fig. 1.—Diagram showing location of nidation site. Area between lines A and C excised at operation.

Fig. 2.—Diagram of cross section taken through line B, Fig. 1, showing relation of maternal blood space to peritoneum and to interstitial portion of tube. Shaded area of anterior myometrium discarded from material subjected to microscopic examination.

the left tube, the left uteroovarian ligament, and the upper part of the broad ligament were utilized to cover the uterine closure. It is to be regretted that the left tube and ovary were not removed together with the affected horn in order to corroborate by microscopic examination their completely normal gross appearance.

The postoperative diagnosis was that of early rupture of an interstitial tubal pregnancy. Since this type of tubal pregnancy usually ruptures at a much later stage of development, the early catastrophe aroused special interest. After fixation in formalin, section of the tissue removed showed a small cavity filled with blood clot about 7 to 8 mm. in diameter related to the peritoneal surface of the posterior aspect of the left uterine horn rather than to the interstitial portion of the tube. The portion of the horn anterior to the tubal lumen was cut away and the remainder was embedded in paraffin (Fig. 2). Serial sections were cut from the entire involved area, every tenth section being saved and stained. The low power photomicrograph (Fig. 3) showed a section through the central portion of the lesion. The peritoneum on the posterior aspect of

## PSEUDOMYXOMA PERITONEI\*

### WITH A REPORT OF THREE CASES

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**P**SEUDOMYXOMA peritonei is an interesting pathologic entity. This condition is characterized by the accumulation of masses of gelatinous pseudomucinous or mucinous material free in the abdominal cavity, and distributed over the peritoneum either as a homogenous layer or in the form of multiple cystic masses. Despite removal of the source and the gelatinous material, repeated reaccumulations may occur, necessitating secondary operations. Ries states, and quotes Werth as stating, that the material must have become part of some organ in the abdomen to be called pseudomyxoma peritonei. It is a relatively rare condition (30 cases in 18 years at the Mayo Clinic, 3 cases in 20 years at the Elizabeth Steele Magee Hospital), seldom seen in patients before the age of 40, and occurring in both males and females, although more commonly in the latter sex.

Peán in 1871 referred to a case of "myxomatous degeneration of the peritoneum" but Werth in 1884 is credited with giving the first description of pseudomyxoma peritonei. Until 1901 it was considered a disease of the female alone, being attributed to rupture of a pseudomucinous ovarian cyst. Then Fraenkel reported a case in a male with the appendix serving as the original focus. Other sources have been claimed; namely, gall bladder, diverticulum of the cecum, umbilical tumor developing from a persistent portion of the omphalomesenteric duct, and dermoid cysts; but in general, the two chief origins are considered to be the ovaries and the appendix. A few cases have been reported in which both a ruptured ovarian cyst and a perforated colloid cyst of the appendix were found. Krivsky is convinced that if both organs are involved, the disease has two distinct and simultaneous places of origin; the one is not a result of the other. Experimentally, pseudomyxoma peritonei has been produced in rabbits both by ligation of the appendix, exclusive of the blood supply, and after irrigation of the lumen, and by the injection of unfiltered pseudomucinous material from a typical case.

This paper deals only with pseudomyxoma peritonei in which the ovaries are the point of origin. Krivsky thinks the prognosis is worse in this form. When a pseudomucinous cyst of the ovary ruptures, the reception of the contents by the peritoneum may be passive with absorption of the contents, or there may occur generalized peritoneal thickening, cellular infiltration, formation of adhesions, proliferation of secondary tumors and formation of multiple cysts; or a combination of

\*Presented at a meeting of the Pittsburgh Obstetrical and Gynecological Society, 1942.

adjacent to the interstitial portion of the tube, but this is believed merely to be accidental. This specimen has been presented before the Society of Gynecological Pathologists of New York. It was the consensus of opinion of the members present that it represented a primary peritoneal pregnancy. In closing, it might be pointed out that Ray<sup>18</sup> in 1921 reported from the Bellevue Gynecological Service an identical lesion on the anterior aspect of the uterus just above the bladder fold. This he believed to be an early primary abdominal pregnancy. Unfortunately this pathologic material was scanty and incomplete, in no way as conclusive as in the present specimen.

#### SUMMARY AND CONCLUSION

An early ruptured pregnancy on the posterior aspect of the uterine horn has been described, which, from its relationship to the peritoneum and to the interstitial portion of the tube, is believed to have reached this location by primary peritoneal nidation.

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Goldzieher and Adler: *Estrogen Treatment in a Female Eunuchoid*, *J. Clin. Endocrinology* 1: 349, 1941.

A case of eunuchoidism and the results of treatment with estrogen are presented. These results are: adequate development of uterus and external genitalia; manifestation of secondary sexual characteristics and establishment of a menstrual cycle; marked development of breasts, attributed mainly to topical administration of estrogen; and striking changes in the general appearance and personality of the patient.

The relationship of infantilism to eunuchoidism is discussed; the latter is defined as a syndrome due to a primary hypogonad state accompanied by secondary hyperpituitarism.

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myxoma peritonei has been noted. The menstrual history may have been regular or irregular. Marital status and parity have no bearing, for whereas all three of our patients were single women, 28 of the 30 patients cited by Masson and Hamrick were married and 21 had had children. Physically the patients usually have a mild secondary anemia, abdominal distention, sallow complexion, and occasionally a cystic mass may be felt on abdominal or pelvic examination.

Treatment consists of two parts: (1) Removal of the source and (2) removal of the pseudomucinous material. Ovarian tumors, whether ruptured or not, should be extirpated, and also the appendix should be removed even if it is so imbedded in gelatinous material that the cecum must be resected. If the uterus is invaded, a hysterectomy is indicated. If there is a nodule in the umbilicus, remove the umbilicus; and if the omentum is involved, it should also be excised. The treatment of the gelatinous material loose in the abdomen and the masses on the parietal and visceral peritoneum is difficult. Washing out is insufficient and complete removal leaves great raw areas. Gentle wiping out is usually resorted to and greater or smaller quantities of material are necessarily left behind. Isolated pseudomyxomatous tumors should be removed as completely as possible. Previous experience dictates that no drains should be left in the abdomen. Finally, x-ray therapy should be given, especially if the pathologist reports malignancy. Hertzler mentions a case in which temporary improvement was coincident with the use of x-ray. Unfortunately, the value of x-ray is neither proved nor easy to evaluate, as the secondary lesions may disappear spontaneously after removal of the source.

It is difficult to be dogmatic about the prognosis of patients with pseudomyxoma peritonei. Ries states that the results of operation may be good at times even though entire masses of gelatinous material could not be removed. He cites a seventeen-year cure. Several cases have been reported of extensive pseudomyxoma peritonei becoming arrested spontaneously and even completely absorbed. There is no explanation for this. Masson and Hamrick believe that if there is no evidence of cancer the outlook is good for permanent cure. Two or three operations may be necessary. However, with the peritoneum diffusely involved, it is impossible to eradicate the growth, and many patients go downhill so that the condition becomes clinically malignant. To quote Ewing, "the evacuation of this material is sometimes followed by remission, rarely by cure, but usually the condition recurs and persists even when very few tumor cells can be found. Interference with intestinal function by adhesions and strictures terminates the prolonged course of many cases." Novak, Douglass and Faulkner, and Karsner agree on this. It is to be noted that all the latter are pathologists.

#### CASE REPORTS

CASE 1.—Miss N. S., aged 42 years, small, frail, emaciated white woman, was admitted Jan. 19, 1928, to the hospital with a complaint of

all these. There may be a different reaction in different parts of the peritoneum. Large amounts of gelatinous material may form, colored in various shades of red, yellow, brown, or grayish white, depending on the amount of hemorrhage, fatty material, cholesterol, and cellular debris.

The mechanism of the continued formation of pseudomucinous material before or after the removal of the primary source is still a moot question. Possibly there has been alternate rupture and closure of the ovarian tumor. Or does direct implantation of epithelial cells from the lining of the original cyst occur? Only occasionally can epithelial elements be found in the colloid masses, but perhaps the epithelial cells originally implanted are crowded out and disappear after having given rise to mucinous material. Can the peritoneal epithelium assume the function of producing mucus? Or is it a metastasis via the peritoneal lymph or blood stream as is undoubtedly the case in secondary cysts found in the liver and portal vein?

Undoubtedly the character of the myxomatous change in the peritoneal walls will vary with that of the primary new growth. For practical purposes, therefore, there may be considered to be two types of secondary pseudomucinous growth: (1) pseudomyxoma peritonei simplex, a benign passive deposit of the pseudomucinous material in the abdominal cavity; (2) pseudomyxoma peritonei malignum, a transplantation of epithelial cells to the peritoneal surfaces, cells which originally may be malignant or take on malignant characteristics. The distinction between malignancy and nonmalignancy depends upon the degree of recurrence. Thus, some cases can be considered definitely malignant with recurrences in as short a period as a few months, others relatively benign, with no recurrence for years; and still other cases benign when there is no recurrence.

Chemically the gelatinous material is alkaline in reaction. Whether the material is acid when the appendix is the focus and alkaline when an ovarian cyst is the focus as Trotter states, is open to question. Also whether the material is pseudomucin or true mucin as based on its staining reaction with mucicarmine or reduction tests is a valueless distinction; all gradations of staining reactions occur, and reduction tests may be obtained with true mucin.

Clinically pseudomyxoma peritonei presents no inconvenience to the patient until enlargement of the abdomen occurs, as simple rupture of the ovarian tumor does not usually produce any noticeable symptoms. Most patients have symptoms for many months before consulting a physician. The chief complaints are fullness of the abdomen, weakness, dyspnea, frequency of urination, loss of weight, anorexia and often abdominal pain. There may be a history of a previous operation for removal of the appendix or an ovarian cyst. An interval of twenty-two years after the primary operation before the appearance of pseudo-

curettage, bilateral salpingo-oophorectomy, and appendectomy. Pathologic diagnosis: Pseudomucinous ovarian cyst, chronic peri-oophoritis.

Physical examination revealed a distended abdomen with a cystic mass on the left side. Red blood count was 3,840,000; hemoglobin, 78 per cent; and white blood count, 10,800. Urinalysis, serology, and blood chemistry were negative.

She was given a transfusion, and operation was performed on Oct. 1, 1928. "Half a pus basin" of pseudomucinous material was removed, also a left cystic structure considered to be part of left ovary and cystic mass of omentum was removed. Pathologic diagnosis: Pseudomucinous multilocular cystadenocarcinoma of ovary and omentum. Postoperative course was uneventful. She remained in hospital twenty-eight days.

*Second Admission, April, 1931.*—She felt well until previous summer. Since then there had been a gradual reaccumulation of fluid in the abdomen, increasing weakness, fatigue, and pressure symptoms.

At operation on May 1, 1931, 4,800 Gm. of orange-colored pseudomucinous material and a piece of peritoneum were removed.

Pathologic diagnosis: Peritoneum with chronic inflammatory reaction.

Postoperative course was uneventful. She was in the hospital fourteen days.

*Third Admission, September, 1931.*—The abdomen had begun to swell shortly after leaving the hospital in May. She was readmitted to drain abdomen. At operation on Sept. 10, 1931, four gallons of gelatinous material were removed. Biopsy of peritoneum was made. Pathologic diagnosis: Papillary cystadenoma malignum of ovary.

Postoperative course was uneventful. She was in the hospital twenty-nine days.

*Fourth Admission, January, 1933.*—There was marked improvement following the last operation, and her state of health has been better than at any time in years. A cyst is still present in the left lower quadrant, the size of a grapefruit. She is so much improved following last operation that she was admitted to attempt a removal of what was probably the primary growth. At operation on Jan. 30, 1933, intestines were matted together and involved in a recurrence of the papillary cystadenocarcinoma. Large quantity of thick jelly-like, yellowish material was removed. Supravaginal hysterectomy was done. The tumor growth was removed from remnants of omentum, peritoneum, colon, liver, and mesentery of small intestine. Colon was perforated.

*Pathologic diagnosis:* Atrophic endometrium, chronic metritis with arteriosclerosis, adenomyoma of uterus, and papillary cystadenoma, secondary. Complication: fecal fistula. Remained in hospital twenty-eight days.

*Fifth Admission, December, 1935.*—Patient felt well up until a few months ago. Since then there had been fullness and discomfort in the abdomen, anorexia, weakness, and diarrhea. Physical examination showed a very pale, well-developed, well-nourished, white female of 64 years. Abdomen was dome shaped. Irregular mass was palpable in the upper abdomen.

Red blood count was 3,300,000; hemoglobin 67 per cent; and white blood count, 9,400. Blood chemistry was negative. Urinalysis showed 1+ albumin.

At operation on Dec. 10, 1935, the intestines were found to be studded with small tumorous nodules; spleen was enlarged and covered with

pain in left groin, epigastric fullness, loss of weight and strength. There was a history of feeling weak and tired, having trouble with hemorrhoids, and loss of 18 pounds during past year. There was a sense of fluid splashing about in abdomen. Menopause occurred 2 years previously. For several months epigastric fullness and anorexia were more pronounced. She had to stop work four weeks prior to admission due to weakness. Physical examination showed the abdomen to be rounded and tense with superficial veins prominent. Fluid wave was present. Red blood count was 3,900,000; Hg, 76 per cent; and white blood cells, 7,400. Urine, blood chemistry and serology were negative.

Operation performed on Feb. 1, 1928, revealed a right ovarian multilocular cyst extending 4 cm. above the umbilicus. Several loops of bowel were adherent. The cyst contained a large amount of amber-colored gelatinous material, and this material was also free in the abdominal cavity, even extending up under the diaphragm. The left ovary was small and atrophic. Gall bladder and appendix were not examined. Cyst and gelatinous material were removed. The incision was closed without drainage.

*Pathologic Diagnosis:* Pseudomucinous papillary cystadenoma of ovary, chronic inflammation of cyst wall.

Postoperative course was uneventful and when seen six weeks following operation, she was feeling well. There was no further follow-up.

CASE 2.—Miss N. H., aged 62 years, thin, frail, white woman, was admitted Sept. 30, 1941, to the hospital with complaint of increasing fullness of abdomen, loss of 15 pounds in past year, and weakness. There was a history of two previous hospital admissions elsewhere: First in 1931 when she had an appendectomy and a right oophorectomy. Pathologic diagnosis: Dermoid cyst of right ovary, multilocular pseudomucinous cyst of right ovary, and chronic appendicitis. Second in 1936 when there was an operation for evacuation of abdominal contents and removal of part of growth. Pathologic diagnosis: Papillary pseudomucinous cystadenocarcinoma of right ovary. Physical examination revealed a tense abdomen with evidence of fluid, and on vaginal examination there was a soft mass in the cul-de-sac and pelvis, or rather multiple small masses.

Red blood count was 4,300,000; hemoglobin, 76 per cent; and white blood count, 4,450. Urinalysis, serology, and blood chemistry were negative.

Operation performed Jan. 2, 1941, revealed two previous laparotomy scars which were excised. Peritoneum was markedly thickened and on the right side of the abdomen there appeared to be a secondary abdominal cavity well walled-off and filled with a yellowish gelatinous material. Seven quarts of this material were removed, and a biopsy was taken of the peritoneum. Abdomen was closed without drainage. Pathologic diagnosis: Peritoneum and skeletal muscle without evidence of tumor, pseudomyxoma peritonei.

Postoperative course uneventful. Patient appears well four months later. X-ray treatments have been given.

CASE 3.—Miss B. S., aged 55 years, a well-developed, well-nourished, pale Jewish female, was admitted to the hospital on Sept. 25, 1928, with chief complaint of mass in abdomen of one years' duration, and progressive weakness. She had been operated upon in another hospital five years previously for "flooding spells." She had a dilatation and

to registration at the clinic, she had begun to experience severe headache at the occiput and vertex, as well as pain in both eyeballs. This pain was associated with stiff neck and ringing, pounding tinnitus in both ears. A week prior to her entering the clinic, nausea and vomiting had begun but were not definitely associated with the headache. Her symptoms had progressed to such an extent, she remarked, that three days before her examination at the clinic she thought she was "going to die," because she had experienced numbness of both hands and arms, and then a wave of numbness, so to speak, over the whole body.

In giving her history the patient stated that in August, 1937, the uterus had been removed after a diagnosis of "hydatid mole" complicating pregnancy. There had been, she was assured, no penetration of the uterine wall. No symptoms had arisen to indicate recurrence of the process locally in the pelvis.

The sudden onset of severe and evident intracranial pressure was very suggestive of tumor of the brain and because of the previous lesion in the uterus, a metastatic malignant process was considered in the preliminary diagnosis. The interval of four years between hysterectomy and the current symptoms, however, seemed to point against recurrence of this type of neoplasm.

Upon examination, the patient was found to have complete left homonymous hemianopia with enlarged blind spots and bilaterally choked disks (elevation of 2 diopters), with hemorrhage of some extent. Neurologic examination revealed some degree of weakness of the left side of the face and of the left extremities, and there was a slight increase in reflexes on the left side. Roentgenologic examination of the head disclosed questionable shifting of the pineal gland toward the left. The electroencephalogram demonstrated a delta localization in the right posterior temporooccipital region. The results of other examinations, including pelvic examination, were negative. A diagnosis of primary tumor of the brain was made and operation was advised for removal of a tumor of the right temporal lobe.

Operation was carried out on Aug. 5, 1941. With the patient under the influence of intratracheal anesthesia, right craniotomy was performed. The convolutions of the temporal lobe were flattened and broadened in the posterior aspect. A mass was found subcortically, and when the cortex was incised, a dark, vascular nodule about the size of a large plum (Fig. 1) was found, at a depth of about 3 cm., extending posteriorly into the occipital lobe. The tumor "shelled out" after the manner of a metastatic lesion, and grossly suggested chorionepithelioma.

After an uneventful convalescence, the patient was allowed to return to her home on the tenth postoperative day. The wound had healed well and the patient was completely relieved of her headache. She still had homonymous hemianopia, however. In a recent communication from the physician in attendance we learned that the patient died on Sept. 19, 1941. There was no necropsy.

*Histopathologic Observations.*—Grossly, the tumor was 6 by 4 by 3 cm., was brownish red, and seemed to have separated cleanly from the surrounding brain tissue. The cut surface demonstrated the nodule to be hemorrhagic, a feature somewhat unusual for cerebral metastasis of chorionepithelioma.

In microscopic sections made by the rapid freezing technique and stained with polychrome methylene-blue, large masses of pale-staining cells were seen. These were manifestly malignant. Intermingled with

tumorous growth; and 4½ pounds of gelatinous material were removed. Pathologic diagnosis: Pseudomyxoma peritonei.

Postoperative course was uneventful. She was in the hospital twenty-one days.

This patient was admitted to another hospital about six months later and died in October, 1936, of intestinal complications resulting from the abdominal tumor.

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### CHORIONEPITHELIOMA\*

#### AN UNUSUAL CASE IN WHICH CEREBRAL METASTASIS OCCURRED FOUR YEARS AFTER HYSTERECTOMY

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WITH considerably more than 2,000 records of chorionepithelioma in the medical literature, an introductory apology is perhaps necessary before we add another. The following unique features in our case would appear to justify inclusion of it among the more unusual and interesting examples of this rare form of malignant process: (1) a four-year period of latency between removal of the primary neoplasm and the appearance of secondary lesions, (2) cerebral symptoms as the first indication of metastasis, and (3) a negative reaction to the Friedman test.

#### REPORT OF A CASE

A woman, 29 years old, came to the clinic in July, 1941, complaining of headache, weakness, and double and blurred vision. Two and one-half weeks previous to her examination, she had noticed rather rapid loss of vision, until only the gross form of objects could be seen. There was marked loss of balance with staggering, but the patient did not fall. Thereafter, blurring of vision recurred frequently. Two weeks prior

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these cells were observed irregular sheets of malignant syncytial cells with abundant cytoplasm and large hyperchromatic nuclei. Glial fibers, always identifiable by the aforementioned method of examination, were not observed. The picture, briefly, was that of a metastatic Grade 4 neoplasm, and was entirely compatible with a diagnosis of chorionepithelioma. Immediately after operation urine was collected on a quantitative basis, for determination of prolan according to the Friedman technique. Results of this test later were reported as negative for excess amounts of the hormone.

Fixed frozen sections made the day after operation on formalinized blocks of tumor tissue confirmed our earlier diagnosis of metastatic chorionepithelioma. The photomicrographs (Fig. 2, *a* and *b*) depict the characteristic features.

#### COMMENT

Chorionepithelioma is a rapidly fatal form of cancer. According to Ewing, the disease usually lasts for from six to eighteen months (with or without hysterectomy). In at least one case it has progressed to fatal termination within thirty-four days of the inception (so far as could be determined) of the lesion. It is most surprising, therefore, to encounter a case like ours, in which there was such a prolonged "latent period." Outerbridge, in an excellent review of this phase of the subject, mentioned some 25 reports of cases in which there was a latent period of more than two years, and 9 cases in which a period of five years or more had elapsed before "recurrence" became manifest clinically. This author admitted, however, the difficulty of establishing with certainty the exact date at which the primary tumor originates. Chorionepithelioma is a complication of pregnancy, but the actual pregnancy which is concerned with the development of the neoplasm may be "concealed" and occur during the supposed latent period. According to Brown, Snodgrass and Pratt, the duration of this latent period can be established accurately only when it follows hysterectomy for the primary neoplasm. These authors presented such a case. Their patient died as a result of metastatic chorionepithelioma nine years after removal of a hydatid mole and seven years after performance of hysterectomy in which a residual primary tumor had not been disclosed. The case recorded by Cary would have a similar category. Spinal metastasis developed three and one-half years after hysterectomy for chorionepithelioma. Dunger's patient died of cerebral metastasis three years after expulsion of a "mole." To this small group belongs our example, in which the so-called latent period of four years is established on a basis of certainty. The explanation for these delayed recurrences in a tumor so manifestly malignant is beyond the present scope of our knowledge. It is paralleled by the still stranger observations of regression of metastasis as occasionally noted in this strange disease.<sup>7</sup>

The incidence of cerebral involvement in chorionepithelioma is difficult of establishment. Clinical symptoms are at times misleading and permission for examination of the brain often is withheld when the patient comes to necropsy. Polasson and Violet listed the incidence of cerebral metastasis as being 9 per cent in a series of 455 cases which included all types of chorioma. Brews reported a series of 14 cases in which the disease was fatal; evidence of cerebral involvement was present in 5 and such involvement was proved by complete necropsy in 4. These figures,



Fig. 1.—Metastatic chorionepithelioma. The dark color and apparent encapsulation are evident.

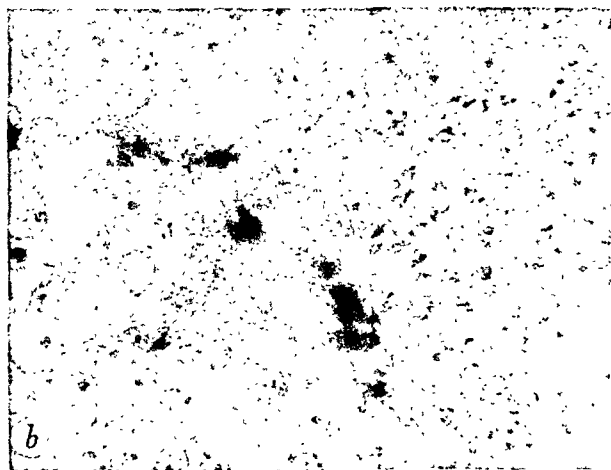


Fig. 2.—*a*, Chorionepithelioma of the brain. The dark staining masses of syncytial cells stand out in contrast to the pale-staining Langhans cells; tumorous tissue is demarcated from the normal brain by a zone of inflammatory cells (hematoxylin and eosin  $\times 70$ ). *b*, Chorionepithelioma of the brain, showing the malignant syncytial (dark) and Langhans (pale) cells in the absence of villous structures (hematoxylin and eosin  $\times 415$ ).



## HYDATID MOLE WITH A HIGH PERSISTENT TITER OF GONADOTROPIC HORMONE\*

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R. M. D., a white married woman 27 years of age, was admitted to the surgical ward of the Episcopal Hospital on Dec. 10, 1940. Her chief complaints were vaginal bleeding and pain in the lower abdomen. Her last normal menstrual period had begun on Sept. 1, 1940, and lasted five days. She had missed her October period. Shortly thereafter she began to experience nausea combined with some sensations of pregnancy. She said that on Nov. 15, 1940, she had lost about a cupful of blood from the vagina within a half hour, but that no further bleeding occurred until December 2, when a little spotting was noted. She again began to bleed on December 5. She is the mother of one child three years of age. There was no other significant medical history.

Inspection on admission revealed a mass which extended above the umbilicus. The mass was movable and not tender, and was believed to be a pregnant uterus. A vaginal examination was not made, since the tentative diagnosis was threatened abortion. Her blood on admission showed 64 per cent hemoglobin and a leucocyte count of 11,000.

I was asked to see the patient in consultation on Dec. 12, 1940. At that time a bimanual examination was performed, and it was noted that the uterus was enlarged to the size of a four and one-half months' pregnancy and that there was no discharge of any nature coming through the closed cervix. At the time of the examination she complained of considerable abdominal pain and looked far whiter than her relatively normal blood count, made on admission, would seem to warrant. I suggested her transfer to the maternity department and made a tentative diagnosis of hydatid mole. Studies of the blood and urine were ordered, and these subsequently confirmed the diagnosis. The patient, however, impressed me as being so anemic that I thought it unwise to wait for the results of these studies to be reported, and immediately began to prepare her for evacuation of the suspected mole. During the next two days she was given transfusions totaling 1,000 c.c. of blood. At this time she was exceedingly distressed with abdominal pain and appeared critically ill.

Evacuation of the mole was performed manually on Dec. 15, 1940, under light ether anesthesia. The entire mole, which amounted to several quarts of grapelike clusters, was removed. There was present in the growth, in addition to the hydatid material, a large number of old and new blood clots.

On the following day the interior of the patient's uterus was gone over lightly with a blunt curette to make sure that complete evacuation had been accomplished. No additional material was obtained.

Convalescence, which was aided by another blood transfusion, was uneventful. The patient was discharged from the hospital on December 29, her blood picture having responded very satisfactorily to the usual treatment.

\*Presented at a meeting of the Obstetrical Society of Philadelphia, December 4, 1942.

although they are higher than the 5 per cent incidence quoted by Green, will still be low when data from complete necropsy become available in large series of cases. Lynch and Maxwell noted a characteristic tendency for localization of metastatic deposits in the occipital lobes. In our case the right occipital lobe was involved, but apparently by a process of extension from a deposit in the temporal convolutions.

Pulmonary involvement, probably always a prerequisite to cerebral metastasis in chorionepithelioma, was not demonstrated by roentgenograms in our case. Peightal, however, recorded an instance in which, with the lungs described as being roentgenographically negative, metastatic deposits were demonstrated therein at post-mortem examination. We hesitate, therefore, in our case, to inject the interesting possibility that the pulmonary focus had disappeared. The inescapable fact of a four-year dormancy in this highly malignant neoplasm carries with it sufficient of the unusual.

The negative reaction to the Friedman test, interesting as it is remarkable, in no wise nullifies our diagnosis in this case. All authorities agree that a *positive* reaction in cases of chorionepithelioma is of prime importance diagnostically as well as prognostically. The reverse, however, is not the case, and many investigators have recorded instances of proved chorionepithelioma in which a single reaction to the Friedman test was negative, or in which a series of positive reactions was interrupted by an occasional negative reaction. Most gynecologists and probably all pathologists will agree with Novak, who asserted that the final diagnosis of chorionepithelioma rests with the microscopist. Admitting that such a diagnosis may be difficult in the case in which only small fragments of tissue or curettings from the uterus are available, histologic evidence of distant metastasis certainly settles the question for all concerned.

#### SUMMARY

A case of chorionepithelioma is presented in which a latent period of four years had elapsed between the removal of the primary tumor and the development of clinical metastasis. The date of inception of the disease was established by the time of a previous hysterectomy. Pathologic proof of cerebral metastasis was furnished by examination of the lesion at biopsy. Urine collected shortly after craniotomy gave a negative reaction to the Friedman test.

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DR. WALT P. CONAWAY.—In June of this year a young girl, aged 19 years, single, was admitted to the gynecologic ward of the Atlantic City Hospital on another service with a diagnosis of hydatid mole. The diagnosis was confirmed and the uterus was emptied with a curette. She made a good recovery and was discharged in about a week.

In July she felt well and the latter part of that month she menstruated five days, apparently normal. At this time the Friedman test was negative. In August and September there was complete amenorrhea but about the middle of October she began to have a bloody discharge with some pieces of tissue. The pain increased for the next few days and she was re-admitted on November 1, this time on our service. Although the uterus was about the size of a ten to twelve weeks' pregnancy, a diagnosis of hydatid mole was made and emptying of the uterus was advised. On account of the severity of the pain and the bloody discharge, a diagnosis of chorionepithelioma was considered. The uterus was again emptied with a curette and the contents proved to be another mole with no evidence of epithelioma. A Friedman test was positive at the time of operation. She bled very freely and a blood transfusion was necessary. After this she made a prompt recovery and was discharged from the hospital in about ten days.

DR. ALBERT P. DAVIS.—I saw two cases of mole this summer, one malignant and one not. The patient with the malignant lesion completed an abortion of the mole on May 26, and kept bleeding off and on, and irregularly, until August 4 when a Friedman test was done which was strongly positive. She re-entered the Hospital, and an hysterectomy was done on August 28. The uterus was about normal in size but in the wall were buried cystic tumors which proved to be a malignant mole on laboratory examination. This patient had another Friedman test on October 27, which was negative. A test before she left the Hospital on September 10 was negative, and another on October 27 was negative, and she now seems to be well.

The other was a case along about the same time. When I first saw the patient she was about three and one-half or four months pregnant. She had had normal children. I suspected a mole because of the condition of the uterus. She was sent into the Hospital. There was no discharge of any great quantity. A Friedman test was negative, and a curettage was done on August 14. An hysterectomy was performed. The test was negative on October 4, and she has remained well. As far as the gross specimen was concerned it was much more positive than the other specimen.

DR. TOLAND (closing).—This case history is presented in order to act as a deterrent to the surgical enthusiasm of those who might desire to remove a uterus shortly after the evacuation of a hydatid mole, merely because a high urinary prolan exists. This report is entirely corroborative of the observations of Payne in his published report of 54 cases of hydatid mole in which urinary prolan was determined after the evacuation or expulsion of the mole, and the patient completely recovered. In his series, which consisted of 8 of his own and 46 collected from the literature, he showed that in all but 5 of the cases, the urine was test negative within eight weeks but that 4 per cent showed positive reactions longer than twelve weeks.

My own case is corroborative of his conclusions that the urinary hormone level will usually return to normal within three months following the termination of a mole pregnancy, "but an abnormal level that persists for a longer time does not necessarily indicate the presence of a chorionepithelioma, provided the level does not rise during this time."

She was referred to the Curtis Clinic of the Jefferson Medical College on February 10, 1941, for quantitative hormonal studies of the blood and urine. Specifically, 330 mouse units of quantitative serum gonadotropin per 100 c.c. of blood were found, and the Friedman test was positive in a dilution of 1 to 10. A re-check two weeks later gave precisely the same high values.

In view of these laboratory findings and the possibility of persistence of the mole or the development of a chorionepithelioma, the patient was re-admitted to the Episcopal Hospital on Feb. 27, 1941. On February 28, under general anesthesia, a diagnostic dilatation and curettage was performed, the latter with a sharp curette. No material of any kind was obtained and there was no bleeding. A check made upon her blood showed 4,300,000 erythrocytes per c.mm., with a hemoglobin value of 80 per cent. She was afebrile throughout, and an x-ray of her chest gave no evidence of pathologic change.

Another study of the patient's blood and urinary hormones in March revealed, to our surprise, the same high titer as in previous tests. A still later study on May 16, however, disclosed that the gonadotropic hormones were then entirely normal in amount.

The patient's menstrual periods returned and, to date (Nov. 21, 1941), have continued normal. The results of a Friedman test made in October have been reported as negative and she is in excellent health.

#### DISCUSSION

DR. A. E. RAKOFF.—I had the opportunity of making the usual hormone assays on this patient during the interval stated. I think the elementary assays which are shown here bring up several points of interest. As Dr. Toland stated, shortly before the uterus was emptied, because of the clinical diagnosis of hydatidiform mole, the serum gonadotropins were very high. That, of course, raises the question as to the value of gonadotropic assays for the diagnosis of hydatidiform mole. Many of these tests were done which at least encouraged us to make an absolute diagnosis of mole on this basis. When we first began making the assays in patients of all kinds, in the first 50 in normal pregnancies, I came to the conclusion that the high value about the third month of pregnancy is usually about 2,000 M.U. per c.c. When the series reached 100, I thought 10,000 occasionally is encountered, and recently we have found in normal pregnancies values as high as 20,000, and that was in a case of suspected hydatid mole. The patient was not operated upon because the attending physicians felt it was not a mole, and their opinion was confirmed. The moral is that this is a laboratory test, is only one piece of evidence, and we do not know how high the serum gonadotropin may go in normal pregnancy. During the first half, they may reach quite high levels, although this value seems to be high enough to be safe. The next factor of interest was after the uterus was emptied, the Friedman test remained positive. This must be viewed with caution because we have found not infrequently that the test may remain positive after a normal delivery in normal patients. Why, I cannot say except pregnancy gonadotropin gradually falls off, and there may be some retained placental tissue viable. The next interesting factor was that the gonadotropin tended to rise somewhat. It would seem here that in time the gonadotropin were at least slightly on the increase and not on the decrease, and the usual assumption is that we are dealing possibly with a chorionepithelioma. In this case this persisted three months, despite the fact that no material was obtained on curettage. The following month the patient menstruated and the gonadotropin returned to normal. What the interpretation is, I cannot say. It does not seem due to the fact that the body is unable to excrete this high amount of gonadotropin. The one assumption is that there was active chorionic tissue present.

TABLE I. SUMMARY OF THE CASES

| AGE<br>IN<br>YEARS | NO.<br>OF<br>CASES | TYPE OF PELVIS |            | AVERAGE<br>HOURS IN<br>LABOR | TERMINATION OF LABOR |                |                 |               |                 |              | OBSTETRIC MORTALITY |                  |               |
|--------------------|--------------------|----------------|------------|------------------------------|----------------------|----------------|-----------------|---------------|-----------------|--------------|---------------------|------------------|---------------|
|                    |                    | NORMAL         | CONTRACTED |                              | SPONT.               | LOW<br>FORCEPS | MID-<br>FORCEPS | CESA-<br>REAN | BREECH<br>EXTR. | VER-<br>SION | MA-<br>TERNAL       | STILL-<br>BIRTHS | NEO-<br>NATAL |
|                    |                    |                |            |                              |                      |                |                 |               |                 |              |                     |                  |               |
| 35                 | 35                 | 31             | 4          | 19.6                         | 17                   | 10             | 5               | 3             |                 |              | 1                   | 2                |               |
| 36                 | 25                 | 25             |            | 24.9                         | 11                   | 8              | 1               | 4             |                 |              |                     | 3                | 1             |
| 37                 | 19                 | 19             |            | 18.9                         | 13                   | 3              | 1               | 2             |                 |              |                     | 1                | 1             |
| 38                 | 13                 | 10             | 3          | 28.3                         | 4                    | 2              | 3               | 3             |                 | 1            | 1                   | 1                |               |
| 39                 | 5                  | 5              |            | 10.7                         | 4                    | 1              |                 |               |                 |              |                     |                  |               |
| 40                 | 8                  | 8              |            | 22.5                         | 4                    | 4              |                 |               |                 |              | 1                   |                  |               |
| 41                 | 4                  | 3              | 1          | 14.3                         | 1                    | 4              |                 |               |                 |              |                     |                  |               |
| 42                 | 2                  | 2              |            | 12.3                         | 1                    | 3              |                 |               | 1               |              |                     | 1                |               |
| Totals             | 111                | 103            | 8          | 18.9                         | 55                   | 31             | 10              | 13            | 1               | 1            | 3                   | 8                | 2             |
| %                  |                    |                |            |                              | 48%                  | 28%            | 9%              | 11.7%         |                 |              | 2.7%                |                  | 9%            |

## THE ELDERLY PRIMIGRAVIDA\*

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THE obstetrician is called upon from time to time to assume responsibility of a case of pregnancy when the woman is having her first baby late in her reproductive life. Both common teaching and experience have led to the belief that the elderly primigravida will have a difficult labor. It has been our experience, however, that because the bony pelvis, from an obstetric point of view, is fixed by the time the young woman enters the childbearing period and the soft parts likewise retain their texture during the entire reproductive period, mere age has a trivial influence on the type of labor.

This study was made in a voluntary hospital with a closed staff (where the majority of cases are handled by general practitioners), in an effort to determine whether there is an increased risk in the labor of the "elderly primigravida." In this group is included the woman thirty-five years of age or over who is pregnant for the first time.

### INCIDENCE

There were 111 such cases among 10,233 deliveries in four and one-half years. The age distribution is given in Table I; the majority were in the 35- and 36-year age group. The pelvis was normal in 103 cases and contracted in 8. It is significant to note the high incidence of normal pelves in this group of elderly patients.

### DURATION OF LABOR

It has repeatedly been stated and indeed it is the common belief that the duration of labor among old primigravidas is usually longer than in the young patient. This is not borne out in this series of cases. The average labor was 18.9 hours (Table I), and is in accord with previous reports of Quigley.<sup>1</sup>

### TERMINATION OF LABOR

Labor terminated spontaneously in 49 per cent of the cases in this series (Table II), while the low forceps operation was employed in 28 per cent. It must be remembered that low forceps is a very common elective procedure in many primigravidas and is practiced frequently. Hence, the number of cases terminated by low forceps should not be over-emphasized in the final conclusions. When one investigates the incidence of major obstetric procedures, the following data are evident. Mid-

\*Read at a meeting of the Bronx Gynecological and Obstetrical Society, April 27, 1942.

Post-partum hemorrhage occurred only once. The patient was treated by uterine packing and transfusion and had an uneventful puerperium.

#### MATERNAL MORTALITY

Three deaths occurred in this series of cases, a mortality of 2.7 per cent. Strikingly enough, they all occurred in patients who were delivered by cesarean section. An analysis of these cases, in all of whom necropsy was performed, showed the following:

1. Death four hours after an operation undertaken for a severe uncontrollable pre-eclampsia. Necropsy showed evidence of liver and kidney damage.

2. One woman died of a bronchopneumonia following evisceration of the abdominal wound on the seventh day post-partum. Necropsy showed bronchopneumonia.

3. One patient died from paralytic ileus without peritonitis. Paralytic ileus was found at post-mortem examination.

TABLE III. OBSTETRIC MORTALITY

| TYPE OF DELIVERY | NECROPSY FINDINGS |                 |                  |           |                     |             |   |
|------------------|-------------------|-----------------|------------------|-----------|---------------------|-------------|---|
|                  | MATERNAL          |                 |                  | FETAL     |                     |             |   |
|                  | PRE-ECLAMPSIA     | PARALYTIC ILEUS | BRONCHOPNEUMONIA | MACERATED | CEREBRAL HEMORRHAGE | PREMATURITY | ? |
| Spontaneous      |                   |                 |                  | 3         | 1                   | 1           |   |
| Low forceps      |                   |                 |                  | 1         |                     |             |   |
| Midforceps       |                   |                 |                  |           | 1                   |             | 1 |
| Version          |                   |                 |                  |           | 1                   |             |   |
| Cesarean section | 1                 | 1               | 1                |           |                     |             | 1 |

#### FETAL MORTALITY

There were eight stillborn infants and two neonatal deaths, giving a fetal mortality of 9 per cent. Four of the stillborn infants were macerated. Excluding these cases, the corrected fetal mortality is 5.4 per cent, an incidence that is at least twice as high as previously reported by us<sup>6</sup> in another study of 10,000 cases at the Bronx Hospital. The fact that this incidence is twice as high entitles it to an important place in the conclusions of this study, whatever causes we may assign to it as an explanation.

#### SUMMARY AND CONCLUSIONS

1. Labor definitely was of no longer duration in the old primigravida.
2. Cesarean section was performed in 11.7 per cent of the cases. It is of utmost importance to note that the age of the patient was not the major indication for the operation, such potent contributing factors as pelvic deformity, progressive toxemia, etc., being present in the cases of the elderly primigravidas in whom cesarean section was performed.
3. The fetal mortality incidence was twice as high among the children born to the older patients as compared with a previous study of 10,000 cases.
4. The maternal mortality was 2.7 per cent.

forceps operations were employed in only 9 per cent of the cases, all in the second stage; 3 cases for persistent occiput posterior; 3 cases for sudden fetal distress; and 4 cases for lack of progress due to maternal inertia (Table II).

Breech presentation occurred four times: 3 were delivered spontaneously and in one case extraction with Piper forceps to the after-coming head was done.

Cesarean section was performed in 13 cases, or 11.7 per cent. This is in accord with the results of Nathanson<sup>2</sup> and Daichman.<sup>3</sup>

The indications for the operation are shown in Table II. In 5 cases the operation was performed because of contracted pelvis; in 3 because of a pregnancy complicating a fibroid uterus; and in 2 cases because of cephalopelvic disproportion. All of these patients had a definite test of labor and the indication for the operation was not the advanced age of the patient. The 3 other cases were elective operations; 2 cases for uncontrollable toxemia, one case for a known cervical stenosis due to a previous cervical amputation.

TABLE II. OPERATIVE CASES

| OPERATIVE INDICATIONS                          | OPERATIVE PROCEDURES |             |          |              |         | OBSTETRIC MORTALITY |       |
|--|----------------------|-------------|----------|--------------|---------|---------------------|-------|
|  | LOW FORCEPS          | MID-FORCEPS | CESAREAN | BREECH EXTR. | VERSION | MATERNAL            | FETAL |
| Head on perineum one hour or more              | 17                   |             |          |              |         |                     | 1     |
| Persistent O. P. or O. T.                      |                      | 3           |          |              |         |                     |       |
| Full dilatation for two hours without progress | 3                    | 4           |          |              |         |                     | 3     |
| Sudden fetal distress                          | 11                   | 3           |          |              | 1       |                     |       |
| Frank breech                                   |                      |             |          | 2            |         |                     |       |
| Contracted pelvis                              |                      |             | 5        | 1            |         | 1                   | 1     |
| Fibroid uterus                                 |                      |             | 3        |              |         |                     |       |
| Toxemia  |                      |             | 2        |              |         | 1                   |       |
| Cervical stenosis                              |                      |             | 1        |              |         | 1                   |       |
| Cephalopelvic disproportion                    |                      |             | 2        |              |         |                     |       |

While an incidence of 11.7 per cent for cesarean section may at first appear to be high and almost suggestive of radical obstetrics, nevertheless, it is of utmost importance not to lose sight of the fact that in the case of the elderly primigravida so much is at stake that everything ought to be done to obtain a living child. It is interesting to compare the results obtained by the so-called conservative clinics. Nixon,<sup>4</sup> of London, reported a series of elderly primigravidas in whom no cesarean sections were performed. Here there was a maternal mortality of 4 per cent and a fetal mortality of 17 per cent; this is a maternal and fetal mortality one and one-half and two times as high, respectively, as that to be reported in this study, notwithstanding our cesarean incidence of 11.7 per cent. Nixon is frank to admit that the operation should have been resorted to oftener in his series of cases. Linden,<sup>5</sup> of Stockholm, who also follows ultraconservative procedures, reports a series of cases in elderly primigravidas in whom craniotomy was performed in 4 per cent of the cases but with no maternal deaths. In our cases the high incidence of cesarean section seems justified. It is evident from the tables that 88.3 per cent were delivered per vaginam.



In 43 cases (27 per cent) the type of previa was lateral; in 78 cases (49 per cent), it was marginal, and in 39 cases (24 per cent), it was central. The ages and parity of the 160 patients are shown in Tables I and II.

TABLE I. AGE OF PATIENTS

|                | NUMBER OF<br>CASES | PERCENTAGE |
|----------------|--------------------|------------|
| 10 to 19 years | 11                 | 7          |
| 20 to 29 years | 69                 | 43         |
| 30 to 39 years | 71                 | 44         |
| 40 to 49 years | 9                  | 6          |

TABLE II. PARITY

|                 | NUMBER OF<br>CASES | PERCENTAGE |
|-----------------|--------------------|------------|
| Para i          | 52                 | 33         |
| Para ii         | 40                 | 25         |
| Para iii        | 19                 | 12         |
| Para iv         | 19                 | 12         |
| Para v          | 13                 | 8          |
| Para vi to xiii | 17                 | 10         |

Pregnancy was complicated in 20 per cent of the cases. The three complications found most frequently were fibromyomas of the uterus, toxemia of pregnancy, and heart disease. It is of interest that three of the patients with previa had had a previous section, and of these two had had previa with the first section.

There were 143 (87 per cent) vertex presentations, 18 (11 per cent) breech presentations, and 3 (2 per cent) transverse presentations. There were 4 sets of twins.

Table III shows the type of delivery used in these cases. In 121 cases (76 per cent) cesarean sections were done. Since 1935 the trans-

TABLE III. TYPE OF DELIVERY

|                                    | NUMBER OF<br>CASES | PERCENTAGE |
|------------------------------------|--------------------|------------|
| Cesarean sections:                 |                    |            |
| 1. Transverse laparotrachelotomy   | 48                 | 30         |
| 2. Longitudinal laparotrachelotomy | 16                 | 10         |
| 3. Low classical section           | 43                 | 27         |
| 4. High classical section          | 12                 | 8          |
| 5. Porro section                   | 2                  | 1          |
| (Total sections 121, 76 per cent)  |                    |            |
| Other methods:                     |                    |            |
| 6. Forceps                         | 19                 | 12         |
| 7. Internal podalic version        | 8                  | 5          |
| 8. Spontaneous                     | 6                  | 4          |
| 9. Breech extraction               | 4                  | 2          |
| 10. Braxton Hicks' version         | 1                  | 0.5        |
| 11. Vaginal hysterotomy            | 1                  | 0.5        |

5. In the last analysis, on the basis of this study, no inflexible rules can be laid down for the routine conduct of labor in elderly primigravidas. Individualization of each case with its concomitant demands would appear to be the only ideal approach to the solution of the problem.

We are indebted to Dr. Meyer Rosensohn for his helpful criticisms in the preparation of this report.

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1229 CLAY AVENUE

1840 GRAND CONCOURSE

### INCIDENCE OF PLACENTA PREVIA DURING A TEN-YEAR PERIOD AT CLEVELAND MATERNITY HOSPITAL (1931-1940)\*

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**M**EDICAL literature has always been full of references to placenta previa. As early as the seventeenth century writers on obstetric subjects accurately described this complication, and its presence has always demanded the wholesome respect of all obstetricians.

Placenta previa is said by leading authorities to occur in from 1 in 200 cases to 1 in 2,000 cases. In the series which we are presenting, those occurring at the Cleveland Maternity Hospital in a ten-year period from 1931 through 1940, the incidence was 160 in 20,498 cases, or one in 128 cases (0.8 per cent). This high incidence is due to the fact that our cases included most of the patients hospitalized from our out-patient department; if the 19,374 deliveries from this department are included, the actual incidence was far less (1 in 249 cases). Of the cases of placenta previa only 19 patients (12 per cent) were Negroes.

Fifty-nine per cent of the patients had no bleeding previous to that for which they were admitted to the hospital. Sixty-seven patients (42 per cent) had pains with bleeding and 21 (13 per cent) were in profound shock. The blood loss was small in 59 cases (37 per cent), moderate in 80 cases (50 per cent), and large in 21 cases (13 per cent). Forty-four patients (27.5 per cent) required transfusions before, during, or immediately after, delivery.

\*Read at a meeting of the Section of Obstetrics and Gynecology of the Academy of Medicine, Cleveland, Ohio, December 17, 1941.

found shock. Forty-four (27.5 per cent) required transfusions before, during, or immediately following delivery.

Sixty-seven per cent were delivered by cesarean section. In the first few years the classical section was commonly performed, but since 1935 the transverse types of laporatrachelotomy has been utilized more and more.

Braxton Hicks' version was used only in one case in which the child was not viable. The Willetts clamp was never used.

The gross maternal morbidity was 37.5 per cent, and the uncorrected fetal mortality was 25 per cent, and there were two maternal deaths (1.25 per cent).

2105 ADELBERT ROAD

## ADENOACANTHOMA WITH OVARIAN METASTASES

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**A**DENOCARCINOMA of the fundus with squamous cell metaplasia is not uncommon. Miller<sup>1</sup> found it in 15 per cent of his cases, while Novak<sup>2</sup> states that it is occasionally seen. The phenomenon is not clearly understood but Novak accepts the origin as from "indifferent" cells "possessing a differentiating potency which under certain conditions can lead to the formation of a squamous type epithelium."

The occurrence of ovarian metastases with fundal carcinoma is uncommon. However, Barnes<sup>3</sup> found it in 7.4 per cent of his cases, Norris and Vogt<sup>4</sup> in 1.7 per cent, and Novak<sup>2</sup> in 4.8 per cent. More uncommon is the appearance in the ovarian metastases, of metaplastic elements with keratin formation. The only other case we have been able to find is the one reported by Schattenberg and Ziskind,<sup>5</sup> which was a far-advanced growth.

The prognosis in adenoacanthoma is apparently little influenced by its strange pathologic picture, although Meigs<sup>6</sup> does not agree in this. The prognosis with ovarian metastases, if not present elsewhere, should be good.

The general lack of appreciation that early carcinoma of the fundus can and does metastasize to the ovary should be a warning to those who advocate only radiation therapy.

### CASE REPORT

H. S., a married, white, multipara, aged 50 years, first came to my (C. T. B.) office on Jan. 16, 1942, with a chief complaint of vaginal discharge. Her family history revealed that a brother and a sister had died of "cancer of the bowel." Her past history was not significant. Onset of catamenia was at 12 years of age, with a twenty-eight-day cycle, lasting five days. She had had two pregnancies (last in 1922), terminated with forceps deliveries at term. Five years ago (1937)

verse laparotrachelotomy has been the most common type of section that we have done in this hospital. In the patients not treated by section manual dilatation was done in 4 (2 per cent), and the Voorhees' bag was used in 3 (1.8 per cent).

The maternal morbidity was 37.5 per cent. The causes of morbidity are listed in Table IV.

TABLE IV. MATERNAL MORBIDITY, 60 CASES (37.5 PER CENT)

| CAUSES             | NUMBER OF CASES | PERCENTAGE |
|--------------------|-----------------|------------|
| 1. Cause unknown*  | 24              | 40         |
| 2. Wound infection | 13              | 22         |
| 3. Pelvis          | 12              | 20         |
| 4. Genitourinary   | 9               | 15         |
| 5. Respiratory     | 5               | 8          |
| 6. Phlebitis       | 5               | 8          |
| 7. Peritonitis     | 2               | 3          |
| 8. Appendicitis    | 1               | 2          |

\*The fever in these cases was of short duration and was not severe.

TABLE V. FETAL MORTALITY

| WEIGHT AT BIRTH        | DEATHS | STILL-BIRTHS | TOTAL | PERCENT-AGE |
|------------------------|--------|--------------|-------|-------------|
| Below 1,500, nonviable | 12     | 5            | 17    | 41          |
| 1,500-2,500, premature | 11     | 4            | 15    | 37          |
| Above 2,500, full term | 4      | 5            | 9     | 22          |
| Total                  | 27     | 14           | 41    | 100         |
| Percentage             | 66     | 34           | 100   | ---         |

The fetal mortality is shown in Table V. The uncorrected fetal mortality rate was 25 per cent (41 deaths in 160 cases). If from this number the nonviable cases and premature deaths are excluded, the corrected fetal mortality was 8 per cent (14 deaths in 168 cases). There were two maternal deaths (1.25 per cent). The first patient had a Porro section; peritonitis and wound disruption developed and the patient died on the twelfth day. In the second patient a classical section was done. Intestinal obstruction and peritonitis developed and laparotomy was carried out on the tenth day. The patient died on the seventy-ninth day with thrombophlebitis and pneumonia.

#### SUMMARY

In the ten-year period from 1931 through 1940, there were 160 cases of placenta previa in 20,498 patients admitted to our hospital (0.8 per cent).

The greatest number were between 20 and 29 years of age, and one-third of them were primiparas.

All of these patients showed bleeding upon admission and 67 (42 per cent) had pain. Twenty-one (13 per cent) were admitted in pro-

nodes; none were found. The patient made an uneventful recovery and was discharged from the hospital on her twelfth postoperative day.

Feb. 16, 1942: First follow-up visit revealed nothing of note.

*Pathologic Report (Dr. Friday).—*"Gross description: The specimen consists of a uterus with attached cervix, both tubes and ovaries. The



Fig. 2.—(33544.) High power. Section taken from the left ovary, showing adenocarcinoma and squamous epithelium which is highly differentiated into the adult type.



Fig. 3.—(33544.) Low power. Section from the left ovary demonstrating the marked keratin formation.

patient began having hot flushes and insomnia, associated with grossly irregular periods. One and one-half years ago she began to spot every day with never anything suggesting a menstrual period. This bleeding stopped in October, 1941, and since then patient had noticed a profuse, serous, malodorous discharge. There was no bleeding of any kind after October, 1941.

Physical examination was essentially negative.

Pelvic examination revealed only a small nodule (3 cm.) at the left cornu of the uterus. This we believed was a myoma.

Jan. 19, 1942: Admitted to Temple University Hospital and a curettage was done. Uterine cavity was found to be three inches deep. Abundant pinkish gray tissue was obtained.

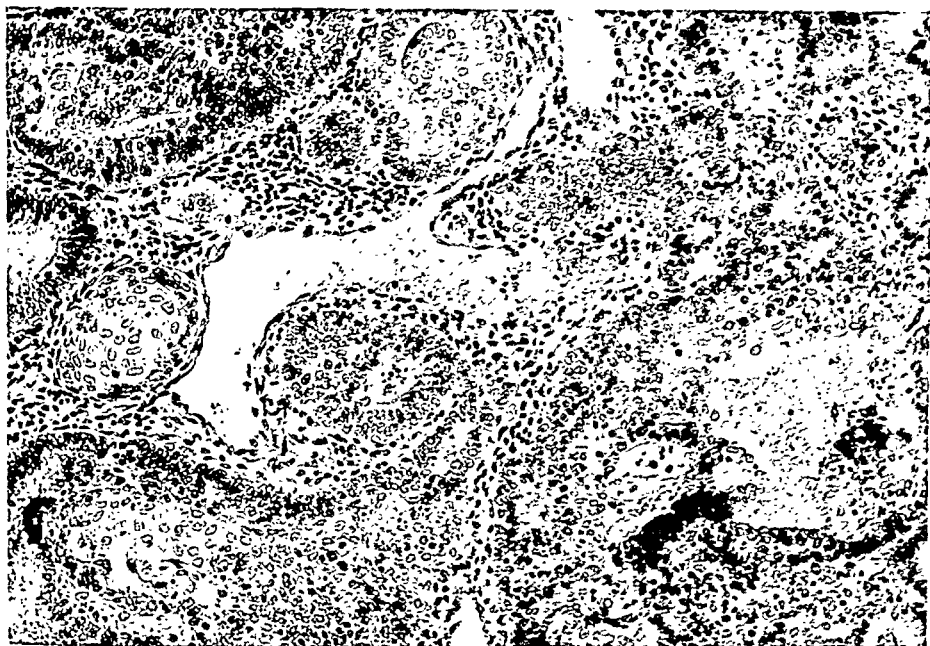


Fig. 1.—(33520.) High power photomicrograph of section from uterine curettings. Note how the squamous cells almost fill the lumen of several glands.

Microscopic examination (Dr. R. H. Friday):

"The uterine curettings show a marked hyperplasia of the glandular elements with loss of the normal pattern and secondary acinar formation. The cells lining the glands are three to four layers deep. They are pleomorphic and hyperchromatic, and in some areas form cordlike projections. There is quite extensive squamous cell metaplasia in some areas, giving the picture of adenoacanthoma.

"*Diagnosis:* Adenocarcinoma, Grade II, with squamous cell metaplasia."

Jan. 21, 1942: Under spinal anesthesia, the abdomen was opened in the midline. The uterus was normal in size, shape, and position, except for one small fibroid. What we had thought was a cornual fibroid proved to be the left ovary which was cystic in part and also demonstrated a hard indurated portion with macular projections from its surface. A radical panhysterectomy and bilateral salpingo-oophorectomy were done. The iliac vessels were exposed and a search made for lymph

## PREGNANCY FOLLOWING OPERATION FOR CONGENITAL ABSENCE OF VAGINA\*

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**C**ONGENITAL absence of the vagina is a rather rare condition. Duckett and Flynn are quoted by Word<sup>1</sup> as being able to find only five hundred such cases in the literature up to 1936, and Word says that about fifty cases have since been described. Other anomalies such as absence of uterus and adnexa and absence of one kidney or the presence of a horse-shoe kidney may be associated with the vaginal defect.

In a recent article Varino and Beacham<sup>2</sup> state that there have been recorded only two cases of unicornuate uterus with complete unilateral absence of broad and round ligaments, tube, ovary, ureter, and kidney of which one is theirs and the other was described by Dannreuther in 1923. The case that I am about to report is a third, which presents in addition to the other anomalies an absence of the left uterosacral ligament and the vagina. Probably because of the close connection of the embryologic development of the urinary with the genital system, anomalies of the two are frequently encountered together. One hundred and twenty cases of congenital absence of one kidney associated with a uterine anomaly are said to have been reported in the literature (Wharton<sup>3</sup>).

The present case is, as far as I am aware, unique in medical literature. It is that of a woman of twenty-one operated upon for congenital absence of the vagina, which was present in association with a unicornuate uterus and a congenital absence of left kidney and ureter, left tube, ovary, round ligament, broad ligament, and utero-sacral ligament. There was also an abdominal left ninth rib. Within a few weeks after operation for the construction of an artificial vagina she became pregnant and was delivered by cesarean section of a full-term living baby.

### CASE REPORT

M. R. (History No. 4596), aged 21 years, white, married, was admitted to the Cambridge Hospital on March 3, 1940.

*Present Illness.*—From the age of sixteen years she had experienced crampy pains every two months, but had never menstruated. At the age of seventeen she had gone to a hospital but no pelvic examination was made. After her marriage three years ago, she had never had successful marital relations. One and one-half years after marriage, however, she began to notice a small amount of blood, apparently about a teaspoonful in amount, that came from the urethra with urination at the time of the regular pains which still appeared at intervals of eight weeks and lasted three to four days. The last episode of such bleeding from the urinary meatus was noted two months ago before her admission to the Cambridge Hos-

\*Presented at a meeting of the Clinical Congress of the American College of Surgeons, Boston, November 6, 1941.

uterus is 6 by 8 cm. Its contour is smooth, except for a small fibroid tumor in the fundal wall. The myometrium is 1 cm. thick. The endometrium is shaggy, granular and hemorrhagic, and thickest at the fundic portion. The growth of endometrium extends to the internal os. The cervix appears normal. The left ovary is cystic and measures 4 cm. in diameter. On the surface there is a small cauliflowerlike projection which feels like keratin. The cyst lining contains several macular projections of similar appearance. The opposite ovary is small and sclerotic. The tubes are grossly normal.

*“Microscopic Examination.*—The sections through the endometrium showed a similar picture as the curettings. There is malignant growth of the glands with invasion of the myometrium to the depth of 3 mm. There is piling up of the epithelium and acinar formation.

“The cervix shows a chronic inflammatory reaction. The predominating infiltrating cell is the lymphocyte. The sections from the left ovary present a curious picture of metastatic adenocarcinoma, with marked squamous cell metaplasia. There is stratification and keratin formation. There is invasion throughout the wall of the cyst. The cells have all the characteristics of malignancy.

“Sections from the left tube show a moderate lymphocytic infiltration and fibrosis of the wall. No tumor cells are visualized.

*“Diagnosis:* adenocarcinoma of corpus uteri; metastatic adenocarcinoma to left ovary; chronic salpingitis (mild).”

#### DISCUSSION

This case of adenocarcinoma of the fundus with squamous cell metaplasia is of interest for several reasons. First, that we have a fairly early, low-grade malignancy demonstrating ovarian metastases. Second, we have found only one other case (Schattenberg and Ziskind) where metaplasia spread to the ovary and produced keratin. Third, the hopeless prognosis this case would have, had we chosen to use only radiation as some clinics propose. Fourth, this case is in keeping with Novak's statement that squamous cell metaplasia occurs “in adenocarcinoma of the lesser degrees of malignancy.”

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5123 WAYNE AVENUE



the right side the shadow of the renal pelvis and the ureter and the kidney excretory function were normal.

Operation was performed on March 18 under cyclopropane, oxygen, and ether anesthesia. A No. 22 metal sound (F.) was first introduced into the bladder and held in the median line. With the left forefinger in the rectum, a two-inch transverse incision was made midway between the external urinary meatus and the anus. By blunt dissection with the finger, the bladder was carefully separated from the rectum, until the cervix was finally felt. Much bleeding was encountered in this stage of the procedure from the perirectal venous plexus. The artificial cavity thus created was enlarged laterally on both sides until the cervix with its external os was visualized and until the cavity would admit to its

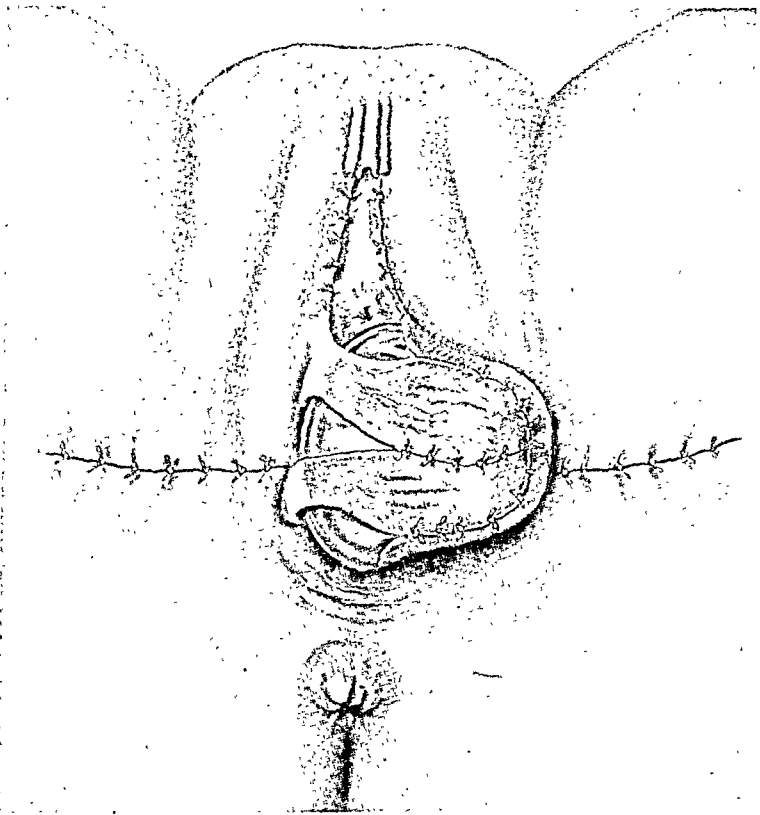


Fig. 2.—The Graves operation. (Reproduced from *Graves Gynecology* by courtesy of W. B. Saunders Company.)

full length a vaginal glass speculum 10 cm. (four inches) long and 3.8 cm. ( $1\frac{1}{2}$  inches) in diameter. The cervix was then seized with tenaculum forceps and pulled downward more into range of vision. At this stage a fistulous tract was seen extending from the upper left side of the portio to the urinary bladder.

Four sutures of No. 1 chromic catgut were placed through the upper and lower quadrants of the cervix and left long. Four plastic flaps were next constructed to serve as a lining for the new vagina as follows: (a) Two flaps of mucous membrane were constructed by partially removing both labia minora beginning at the clitoris and dissecting them down to a point just above the orifices of Bartholin's glands, including a broad pedicle at the base of each flap. Each of these was

pital. The patient had no knowledge of any congenital defects in ancestors or siblings.

*Physical Examination.*—On examination the following points of interest were noted: The breasts showed normal development and there was a normal distribution of axillary and pubic hair. Over the heart, which was otherwise normal, could be heard a soft, blowing murmur at the apex, which was not transmitted. An abdominal rib (ninth) on the left side extended across the abdomen nearly to the midline. The liver, kidneys, and spleen were not felt. The external genitals were normal anteriorly with well-formed clitoris, external urinary meatus, and labia minora. No perineal body was present, and there was no vaginal orifice. On rectal examination the finger brought anteriorly came up against the urethra, with only the rectal wall intervening. The cervix was easily felt and the uterus found to be small but of normal size and consistency, in good position but somewhat to the right of the midline. Urine and blood examinations were negative.

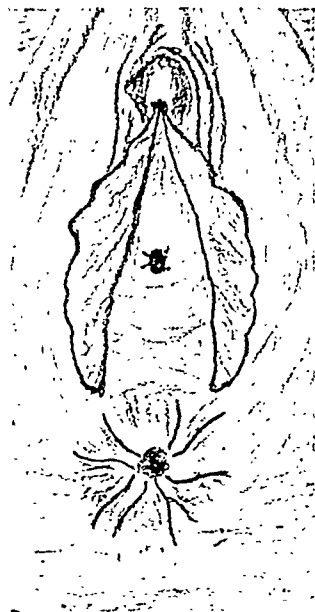


Fig. 1.—Drawing of congenital absence of vagina in Patient M. R.

Cystoscopy was performed by Dr. Harold Chamberlin on March 7, 1940. This examination revealed a normal bladder mucosa and a right ureteral orifice in the usual position. The right ureter was catheterized and a pyelogram made. The left ureteral orifice was not seen and the left angle of the trigone was noted as poorly defined.

Two days later the patient began to pass a slight amount of blood in the urine on voiding, representing her menstrual period. Urethroscopy and an intravenous urogram were made during the catamenia. Through the cystoscope several small reddened areas were seen in the trigone and bladder base but no bleeding from these areas was noted. On urethroscopic examination, moderate oozing of blood appeared to come from the urethral floor to the right of the midline, but no opening could be seen at this point. Pyelograms failed to demonstrate any kidney shadow on the left side and intravenous urograms confirmed this finding. On

the removal of the catheter in the hospital, there had been occasional urinary incontinence, normal control of urine was now attained.

A definite menstrual period occurred on June 27, and a very slight flow on August 7 which lasted only two days. Morning vomiting occurred several times, and on September 19 the uterus was found to be definitely enlarged and lying to the right of the midline.

From this point pregnancy progressed normally with occasional symptoms of slight incontinence. On March 10, 1941, rectal examination showed the cervix to be one and one-half fingers dilated, but the patient was advised to enter the hospital for cesarean operation. She was admitted on March 18, 1941, just one year after the operation. The indications for an elective cesarean operation were the rather rigid, narrow artificial vagina, with congenital absence of the perineal body. There was also the question of the strength of the uterine wall because of the supposed absence of left adnexa and ligaments.

Cesarean section was carried out on March 19 under spinal anesthesia through a right paramedial incision. The right rectus muscle was retracted outward and the peritoneum opened without incident. The uterus was incised between stay sutures and the incision enlarged with bandage scissors. A normal child, weighing five pounds, nine ounces, was delivered by the breech, and an anteriorly placed placenta with membranes was removed. The uterus was closed with three layers of No. 2 chromic catgut.

The uterus was next delivered and examined. There was now noted complete absence of the left adnexa, the left round ligament and broad ligament, and the left uterosacral ligament. The right tube and ligaments were normal, but the right ovary was somewhat elongated and larger than usual. The condition was therefore a true uterus unicornis. Palpation revealed also an entire absence of the left kidney. The abdominal wall was closed in layers without drainage and the patient returned to bed. She made an uneventful recovery and was discharged with the baby, both in good condition, on April 3, 1941.

Following this operation, the catamenia occurred at regular intervals of thirty to thirty-three days and lasted three to five days with rarely slight pain for the first twenty-four hours. Urinary incontinence had disappeared. She menstruated for the last time on Sept. 3, 1941, and vomiting again appeared in the mornings. A vaginal examination on Nov. 15, 1941, showed an introitus that easily admitted one finger to its full length, the caliber of the vagina being about one and one-half fingers. The external meatus could not be seen because it was drawn up beneath the symphysis by slight contraction of the anterior vaginal wall, and there was no perineal body. The cervix was definitely softened. The uterus was up at a good angle but somewhat to the right of the median line and enlarged to the size of a two months' pregnancy.

One other case of pregnancy following the construction of an artificial vagina was found in the literature. Wagner's<sup>5</sup> case reported in 1923 followed a Schubert operation, and differs from mine in the very important respect that there was present a small but definite vaginal canal with an opening which allowed the passage of menstrual blood. In my case there was no external opening at all, the only avenue for the escape of menstrual blood being the fistula extending from the left side of the portio to the vesical floor. In my case the blood was evacuated only when the patient relaxed the vesical sphincter muscle to micturate. For this reason only, my patient did not develop hematometra.

broadened out into a butterfly shape by incising the raw surface in its long diameter. (b) Then a flap was dissected from the inner aspect of each thigh consisting of the entire thickness of skin and subcutaneous fat. The four flaps were sutured together over an old-fashioned glass vaginal speculum as a form, thus constructing a tube with an orifice at its apex to fit about the cervix after the method devised by William P. Graves.<sup>4</sup> The four sutures of No. 1 chromic catgut which had been placed at the four quadrants of the cervix were threaded on a curved needle and brought through each of the four flaps near its apex. When these sutures were about to be tied, the glass form was removed and the entire tube was inverted, forming a lining for the artificially constructed vagina which was then packed with gauze overlaid with rubber dam.

Sterile dry dressing, pads, and T-binder and bandages were applied and a self-retaining catheter placed in the bladder. Since the patient had lost considerable blood from general oozing from the perirectal veins, she was given a transfusion following the operation.

The postoperative course was characterized by several minor complications, but the artificial vagina itself healed well. The pack was removed from the vagina on the second postoperative day. On the third day the catheter apparently became kinked and the dressing became saturated with urine. On the fourth day, since the hemoglobin was only 57 per cent and the red blood count three million, a second transfusion of 500 c.c. of blood was given. An oil retention enema and milk of magnesia by mouth were also given on this day. On the eleventh day the self-retaining catheter slipped out and the patient voided spontaneously.

The thigh wounds were noted as reddened as early as the third day, and by the seventh these began to gape. The left thigh flap had come out of the vagina and was partly necrotic. On the next day both thigh flaps had come out of the vagina and there was an increase in the purulent discharge. The perineal wound remained fairly clean and on the eleventh day the edges were approximated with adhesive bridge and the granulations sprayed with aristol powder. The labial flaps took well and on April 4 it was possible to insert a finger into the vagina and feel the cervix.

On April 5 under cyclopropane anesthesia a secondary closure of the thigh wounds was carried out. Granulating areas on the inner aspect of each thigh were curetted, the skin undermined above and below, and the skin edges freshened. Approximation of the edges was accomplished with pulley sutures and by plain interrupted sutures of heavy silk. This opportunity was also taken to dilate the artificial vagina.

The convalescence from the second operation was complicated by a left parotitis which developed on the fourth postoperative day. Sulfanilamide and x-ray treatment were given and the swelling disappeared in five or six days. The thigh wounds now healed satisfactorily and the patient was discharged on April 24, 1940.

As a result of my experience with this operation, I should in the future use only the labia minora to line the artificial vagina and not try to employ skin flaps from the thighs.

During the following six months the patient came to the office at bi weekly intervals for dilatation of the artificial vagina. Coitus with normal orgasm was reported to have occurred five days after discharge from the hospital. Menstruation began on May 25 and lasted four days with a good, normal flow from the vagina. Although at first, following

interference with the circulation but possibly to a disturbance in the water metabolism. This opinion is substantiated by the case reported here, where, in the presence of a very large ovarian fibroma, there was a fair amount of fluid in the peritoneal cavity as well as a marked subcutaneous edema confined only to the region of the lower abdomen. There was no edema of the lower extremities and no evidence of hydrothorax. In the absence of any evidence of cardiovascular pathology, a localized edema of such nature may be due to some disturbance in the water balance of the system.

#### CASE REPORT

P. S., a 41-year-old colored female, was admitted to the Beth Moses Hospital on March 4, 1941, with a history of irregular vaginal bleeding, weakness, and loss of weight. Two years ago her menstrual period, which was on time, lasted for twelve days instead of the usual five days; it was very profuse and was accompanied by passage of clots. She was admitted to the Kings County Hospital, Brooklyn, where she was told that she had a tumor. When the bleeding ceased, she signed a release. Three months later the patient had another episode of bleeding with passage of clots, lasting for one week. Since that time she has menstruated about every two months, the flow lasting from seven to eight days; it was very profuse with passage of clots. There was no dysmenorrhea. Three weeks prior to admission she felt dizzy and developed a slight cough. One day later she had a watery vaginal discharge. Eight days later she began to bleed profusely, the bleeding persisting until admission to the hospital. The patient was a gravida ix, para vi. She had had three miscarriages following the birth of her first child. Her youngest child was thirteen years old. The patient's menses started at the age of 13, occurred every thirty days, and lasted for five days. There was no dysmenorrhea or leucorrhea. The patient was suffering from constipation, her appetite was poor, and she had lost 80 pounds during the past year.

Physical examination revealed an acutely ill woman, cachectic and pale. Her blood pressure was 138 systolic and 76 diastolic. Heart examination revealed essentially negative findings. The lungs revealed the breath sounds clear. There were no râles or evidence of any fluid in the thoracic cavity. Abdominal examination revealed a visible and palpable mass filling the entire abdomen from the symphysis to the ensiform. The mass was slightly movable, hard, nodular, and not tender. The skin over the lower abdomen was leathery in consistency and edematous with marked pitting on pressure. There were dullness, anteriorly and tympany in the flanks. There was no evidence of shifting dullness. There was no edema of the legs. Vaginal examination revealed a multiparous outlet. The cervix was high in the vault of the vagina; it was lacerated, movable, and not tender. The uterus could not be felt independently of the abdominal mass. The adnexa could not be palpated. The general appearance of the patient, the anemia, the loss of weight, and the nodular feel of the abdominal mass suggested the presence of an ovarian malignancy.

*Laboratory Findings.*—Urine was essentially negative. Blood count revealed hemoglobin 6 Gm. per 100 c.c.; red blood count, 2,470,000; white blood count, 10,200; polynuclear leucocytes, 65 per cent; and lymphocytes, 35 per cent. Wassermann and Kahn tests were negative.

## SUMMARY

This is a report of a case of successful childbearing following an operation for the construction of an artificial vagina in a patient who presented the following anomalies: Agenesis of the vagina, left tube and ovary, left round ligament, left infundibulopelvic and left uterosacral ligaments, together with agenesis of left kidney and the presence of an abdominal ninth rib on the left side. In this case the Graves' operation for the construction of an artificial vagina was eminently successful, although a modification in the technique has been suggested. The patient is now pregnant for the second time.

It is very important in the aftercare of patients operated upon for vaginal agenesis to stretch the artificial vagina twice weekly for six months. If they are married they should have coitus twice weekly during this time. The tendency to contraction of the artificial vagina, however, is over at the end of six months.

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3 CONCORD AVENUE

## FIBROMA OF THE OVARY

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OVARIAN tumors are very often associated with ascites. In cases of ovarian fibroma, the ascites is sometimes accompanied by hydrothorax. This symptom complex was first described by Meigs and Cass<sup>1</sup> and since then has been known as "Meigs' Syndrome." In his original report Meigs stated that he had no adequate physiologic explanation for this phenomenon. Bomze and Kirschbaum<sup>2</sup> suggested that the ascites and pleural effusion may be the result of a low-grade cardiac decompensation in a patient who has a subclinical or compensated cardiac weakness in which the cardiac reserve is just sufficient to withstand the strain of the patient's activities. The added stress thrown on the heart by the pressure of the heavy ovarian fibroma, combined with its possible interference with pelvic and lower abdominal circulation, may be sufficient to produce the low-grade cardiac decompensation. This view does not account for the fact that often the tumor may be small, hardly sufficient to interfere with the circulation by virtue of its weight or size. Neither does it explain the fact that the mere removal of the tumor is sufficient to bring about the disappearance of all the fluid as well as the complete recovery of the patient without any treatment being directed toward the cardiovascular system.

It would seem that the accumulation of fluid in the abdominal and thoracic cavities of patients with ovarian fibroma is not due to any

present a pearly-gray color with mottled yellow and tan areas. A cortical zone was rather well demarcated because of the presence of numerous 0.2 to 0.3 cm. sized grayish nodules. The left tube measured 15 cm. in length; its fimbriated end was also patent. A lappet of tissue, 5 by 3 by 2 cm., was adherent by tuboovarian ligament to the left tube. Contiguous with this mass, but demarcated from it somewhat, was a mass, 21 by 18 by 11 cm. This mass presented a smooth capsule. The surface vessels were distended and prominent and a number of bosses, representing the domes of cysts and containing clear to serohemorrhagic fluid, were noted. The remainder of the mass was solid except for innumerable spongelike areas presenting a reddish gray color. The solid portions of the mass presented a pearly gray color with circumscribed nodular areas and whorls of tissue resembling a fibromyoma of the uterus. The left ovarian mass weighed 2,270 Gm. without fluid evacuated and lost during the course of the operation.

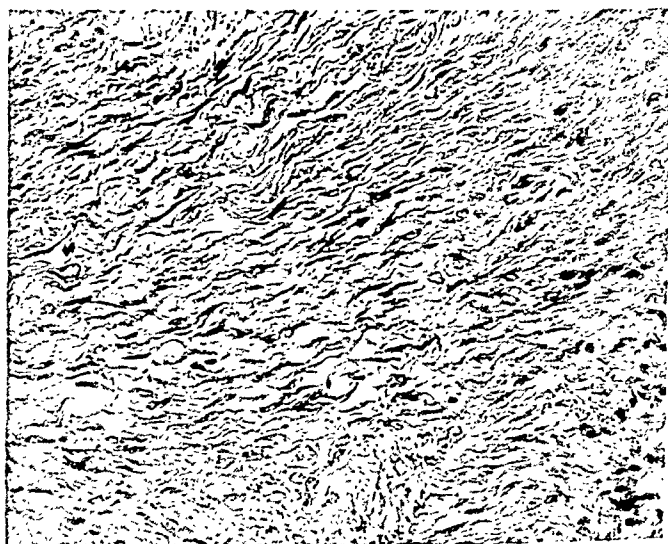


Fig. 2.—Microphotographs of ovarian fibroma, showing interlacing bundles of spindle cells.

*Microscopic:* The endometrium was in a stage of proliferation. The polyp was composed of endometrial stroma and glands. The tubes showed no essential changes. The right ovary showed a hyperplasia of the cortical layer. The mass in the left ovary was composed of interlacing bundles of spindle cells. There was no atypism. A rare mitotic figure was noted. Sudan stains revealed no fats. Doubly-refractile bodies were not found. The van Gieson and other fiber stains revealed only a collagen network of fibrils; no cytoplasmic network. Areas of degeneration and necrosis with cyst formation were noted. The lappet of left ovarian tissue was normal.

*Diagnosis.*—Large fibroma of the left ovary; hyperplastic right ovary; proliferating endometrium; Graafian follicle (left ovary); endometrial polyp.

The patient's postoperative stay in the hospital was longer than usual. There was a rise in her temperature to 103.4° F. on the third day. This lasted for three days, subsiding after sulfathiazole medication. The

Blood chemistry revealed sugar 85 mg., urea nitrogen 8 mg., and chlorides 470 mg.

The patient received two transfusions of 500 c.c. each on the third and fifth days of her stay at the hospital. Her hemoglobin then rose to 9 Gm. per 100 c.c. and red blood count to 3,780,000.

Two days later a laparotomy was performed. At operation marked edema of the subcutaneous fat was found. There were about 500 c.c. of straw-colored fluid in the peritoneal cavity. The left ovarian tumor was the size of a basketball; it was twisted upon its pedicle and was solid in consistency, except for a few cystic areas. The uterus was slightly enlarged. The right ovary was solid, the size of a hen's egg. There was no evidence of any peritoneal or intestinal implantations.

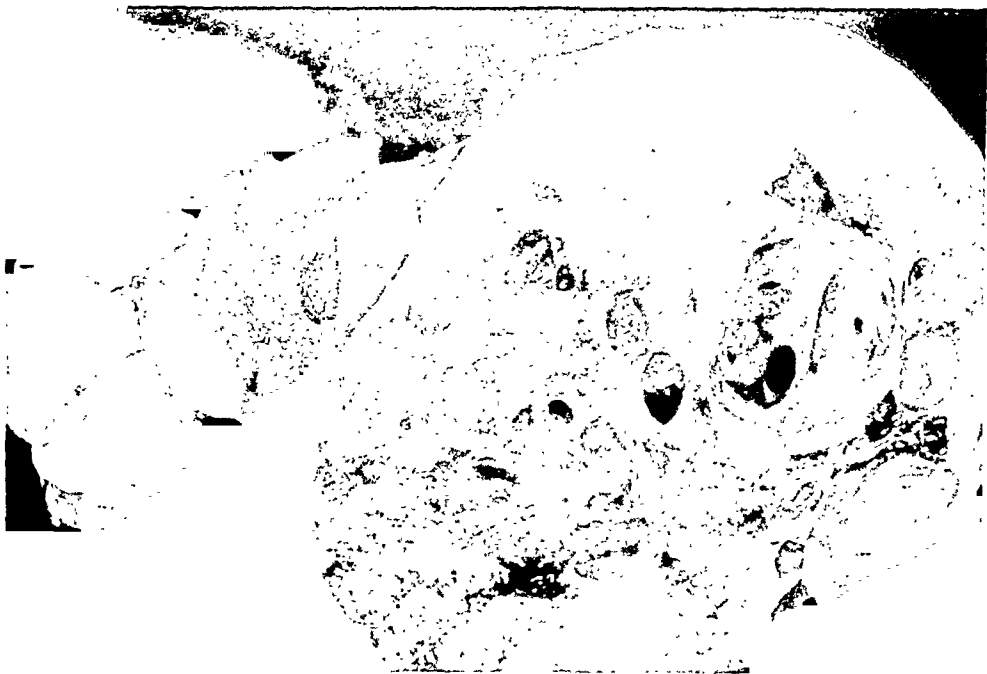


Fig. 1.—Cross section of left ovarian fibroma. Uterus opened, exposing endometrial cavity with small endometrial polyp. Cross section of right ovary.

In order to deliver the cyst, the abdominal incision had to be extended above and to the left of the umbilicus. The cyst ruptured at one point and some thick mucilaginous fluid escaped. A hysterectomy and bilateral salpingo-oophorectomy were performed.

The following is the pathologic report of the specimen, as described by Dr. A. R. Kantrowitz:

*Gross:* Specimen consisted of a supracervically amputated uterus, together with both tubes and ovaries. The uterus was regular in size, measuring 6.5 by 6 by 4.5 cm. The endometrial cavity measured 5 cm. in length. The endometrium presented a mottled hemorrhagic appearance. In the left posterior wall, 1 cm. from the fundus, there was a polypoid projection, 2 by 1 cm. The polypoid projection presented a mottled hemorrhagic appearance. The right tube measured 10 cm. in length; its fimbriated end was patent. The ovary measured 5.5 by 4 by 2.5 cm. It was firm in consistency and on cross section was found to



She had the usual breast and urinary changes of early pregnancy. Nausea was constant and vomiting had occurred twice. There was occasional discomfort in the right lower abdomen.

Physical examination revealed a well-developed young female with findings consistent with pregnancy and with normal pelvic measurements. Hinton test and urine were negative. Blood pressure was 130/70. Usual and present weight was 132 pounds. The following findings were of interest: The patient had a moderate amount of black hair on her upper lip and chin; the arms and legs were unusually hirsute with male distribution upon the pubis. The uterus was boggy, retroverted, being felt in the pouch of Douglas, and a slightly tender egg-sized right adnexal mass was felt. A diagnosis of early uterine pregnancy and right ovarian cyst was made.

Two weeks later the patient was having considerable trouble with nausea and vomiting, she had lost four pounds, and acetone was present in her urine. Thiamin chloride and phenobarbital were administered. A week later her nausea and vomiting had improved, but she was having more frequent and severe pains in her lower abdomen. Examination revealed the ovarian cyst felt in the pouch of Douglas and it had increased in size.

On April 15, a month after her first visit, she reported with severe lower abdominal cramps (both sides) of two days' duration, "sore back," and constant pressure in the rectum. A mass could easily be palpated in the left lower quadrant. Rectal and vaginal examinations showed a grapefruit-sized mass blocking the pouch of Douglas; the pregnant uterus appeared to be anterior.

Laparotomy was performed the next day under ether, eighty-eight days after her last menstruation. A pregnant uterus of about three months' size presented. On the right side anteriorly was found a dermoid cyst about the size of a baseball, containing a large corpus luteum. This cyst was loosely twisted upon itself several times, but there were no signs of interference with the blood supply. Further exploration revealed a dermoid cyst of the left ovary, the size of a baseball, lying in the pouch of Douglas. Both tumors were excised at their pedicles, it being impossible to conserve any ovarian tissue. The patient made an uneventful recovery and continued her pregnancy. For financial reasons, no progesterone was administered. The pathologist reported bilateral dermoid cysts.

Fetal activity was noted during the first half of June. An attack of nervousness and rapid heart occurred during the seventh month. The last two months were characterized by pyelitis (first the right, then the left side), coryza, and sore throat.

Ten days from term the patient felt so uncomfortable from abdominal pains and recurrence of nausea that she was sent into the hospital for induction of labor. Her weight was only 136 pounds, a gain of 4 pounds.

Castor oil and quinine were administered, and since the head was deeply engaged, the membranes were ruptured. The cervix was not taken up or dilated (although rectal examination at home had seemed to indicate cervix well taken up). Within two days labor had not begun, whereupon several courses of pituitrin (minims 1) were administered at forty-five-minute intervals for several hours without results. Two ampoules of synthetic vitamin K were also given.

condition was diagnosed radiographically as a right pneumonitis. The patient subsequently ran a subacute temperature from 100° to 100.2° F. due to an infection of the wound. This finally healed, and she was discharged from the hospital twenty-two days postoperatively in good condition.

#### SUMMARY

1. A case of large fibroma of the ovary is reported.
2. In addition to a small amount of fluid in the abdominal cavity, the patient had a marked localized edema of the subcutaneous tissue of the lower abdomen.
3. The possibility of fibroma of the ovary causing a disturbance in water metabolism is postulated.
4. Patient's history and clinical findings were strongly suggestive of malignancy. The value of surgery in cases thus diagnosed is once more emphasized.

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### BILATERAL OVARIAN DERMOID CYSTS COMPLICATING PREGNANCY TREATED BY BILATERAL OOPHORECTOMY\*

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**F**ORTY-FOUR cases of bilateral dermoid cysts complicating pregnancy have been reported, of which 13 occurred during the first three months.

In 1938 Bernard Notes<sup>1</sup> of Washington, D. C., reported a case. He stated that a search of the literature revealed but 3 others.

In 1940 Andrews and others<sup>2</sup> of Norfolk, Va., reported a case and culled the literature to such an extent that they discovered 43 others, reports of some of which were incomplete. In this presentation, I wish to offer the forty-fifth and the fourteenth during the first trimester.

#### CASE REPORT

Mrs. E. C., a 25-year-old primigravida, first presented herself at the office on March 16, 1940. Her last period was Jan. 19, 1940, making her due, by dates, Oct. 26, 1940.

Her past history was negative. Her mother had died of intestinal cancer. Catamenia began at 12, occurred every thirty to thirty-five days with a scanty three-day flow, characterized by cramps and a bearing-down sensation premenstrually and on the first day of flow. Her last menstruation was a twenty-five-day interval period with the flow about half the usual amount.

\*Presented at a meeting of the Obstetrical Society of Boston, January 20, 1942.

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## PRIMARY OVARIAN PREGNANCY

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**A**LTHOUGH the number of cases of ovarian pregnancies reported in recent years has increased greatly, the occurrence is still rare enough to warrant the reporting of every case.

We wish to report here what we believe to be a case of true primary ovarian pregnancy. It is generally considered that the pregnancy is of short duration and the early death of the embryo is due to hemorrhage with a rapid degeneration of the embryo. Spears<sup>1</sup> has stated that "the most usual course of ovarian pregnancy is an early ovarian abortion. This is followed by slight or severe intraperitoneal hemorrhage. The embryo is rarely found in these ovarian abortions, but chorionic villi are." Our case is of greater interest because an intact embryo was seen within the ovarian hematoma cavity.

### REPORT OF A CASE

Mrs. M. C., a 29-year-old American housewife, entered the Chester Hospital on the gynecologic service of one of us (W. B. E.) on March 10, 1941, with the complaints of dysmenorrhea and irregular menses of several months' duration. Her last normal menstrual period had been on Jan. 28, 1941, eight days late, and lasted her usual duration of eight days. One week later she again had some bloody show, passing several clots. Soon after this, under medical treatment, she ceased bleeding, but was advised to see one of us (W. B. E.) because of a retroverted uterus and what was thought to be a tumor on the uterus. At the time of her entry into the hospital, the patient was alert and resting comfortably in bed. The blood pressure was 150/90; heart and lungs were clear; the abdomen was flat, soft, and not tender; there was a questionable mass in the right lower quadrant extending toward right flank, and on vaginal examination a mass was found in the right adnexal region. The past history was nonessential. She had had three full-term pregnancies, one of the children having died.

*Diagnosis.*—Right ovarian cyst.

Laboratory data were not unusual and on March 12, 1941, she was operated upon under gas-ether anesthesia. The abdomen was opened through a midline incision. A pedunculated mass about the size of a fist was found replacing the right ovary, and this mass had gravitated into the cul-de-sac where it was adherent. The tumor mass was dissected free and removed along with the right tube which appeared grossly normal. The abdomen was closed in layers with one drain in the pelvis. The appendix was also removed.

*Postoperative Diagnosis.*—Right dermoid cyst.

### **PATHOLOGIC REPORT (DR. G. SICKEL)**

Specimen consisted of a mass 7.5 by 7.5 by 4 cm. which was removed from the right adnexal region, and was accompanied by the right tube

\*Deceased.

Four and one-half days elapsed before strong labor pains set in following a course of pituitrin. The pains were frequent and unusually severe. The cervix became  $4\frac{1}{2}$  fingers' dilated, but no more. Despite tetanic contractions, the head had not descended at all and remained L.O.P. in midpelvis. The fetal heart rose to 170, and the patient showed signs of exhaustion.

Accordingly an intravenous glucose administration was started, and on October 22, under ether anesthesia, delivery was accomplished by right mediolateral episiotomy, Dührssen's incision of cervix, manual rotation, and midforceps. The outer fibers of the sphincter ani muscle were lacerated during delivery and were sutured during the repair of the perineum. The male infant weighed 7 pounds 2 ounces and was 20 inches long. The puerperium was uneventful and afebrile with good healing of cervix and perineum. The supply of breast milk was plentiful, the baby weighing  $31\frac{1}{2}$  ounces over birth weight upon discharge on the fourteenth day. The mother nursed the baby until six weeks post partum at which time lactation was insufficient.

Six months post partum the patient experienced three days of typical menstrual flowing without pain. An endometrial biopsy was taken in the office which showed atrophic endometrium.\* No cause could be demonstrated for the flowing. It had the appearance of menstrual discharge.

Eleven months post partum (September, 1941) she stated there had been no more vaginal bleeding. Hot flushes had been occasional up to the past week, since when they were severe. She felt nervous. Her weight had increased to 146 pounds. Phenobarbital in small doses was recommended.

In conclusion, information concerning the stage of pregnancy, treatment, and outcome of all 44 cases is not available. Andrews has assembled an interesting table in which bilateral oophorectomy was performed in pregnancy, irrespective of cause. Including this case, there are 14 described as performed during the first trimester; of these 11 carried on to term, 3 aborted.

#### SUMMARY

A case of bilateral dermoid cysts complicating pregnancy is presented in which bilateral oophorectomy was performed during the first trimester. The patient was delivered with difficulty at term of a live baby which she nursed for six weeks. Six months post partum menstrual-like bleeding occurred for three days. An endometrium biopsy taken at this time revealed an atrophic endometrium with no apparent cause for bleeding. There has been no recurrence. Otherwise the surgical menopause has been typical.

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84 SPRING STREET

\*The endometrial biopsy was examined by A. T. Hertig, M.D., pathologist for the Boston Lying-in Hospital.

about six weeks old. Along the periphery of the mass an old corpus luteum could be seen, but most of the mass was infiltrated with blood. The tube measured 5.5 cm. in length and had been removed in two pieces. The fimbriae were intact and open, and there was no evidence of a rupture in the tube. Microscopic sections consisted largely of blood clot with an area at the periphery which showed ovarian stroma and the remains of a corpus luteum and corpora albicantia. The tube was not sectioned. Within the sections of the blood clot were found a few chorionic villi.

### CONCLUSIONS

This case is reported as an unusual case of primary ovarian pregnancy in which an embryo, estimated to be of about six weeks' gestation, was found intact within the ovarian hematoma. The case fulfills all the requirements as laid down by Spiegelberg, and although the tube was not serially sectioned, it appeared to be intact grossly. We present this as a case of true primary ovarian pregnancy, but its actual proof and the original distinction between primary and secondary types we leave as an open question.

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Grace and Suskind: *The Treatment of Venereal Lymphogranuloma With Sulfanilamide*, *Ven. Dis. Inform.* 13: 26, 1940.

Since 1932, 229 cases of venereal lymphogranuloma were studied by the authors. A number of therapeutic procedures were employed and the best results were obtained following the use of sulfanilamide.

Ambulant patients were given the drug in comparatively small doses over a period of three to seventy-six weeks with intermittent rest periods. Hospitalized patients received larger doses for six to twenty-three days. The total amount of sulfanilamide administered to the inguinal cases varied between 37.8 and 82.8 Gm. and to the anorectal cases between 34.2 and 584.1 Gm.

Four of the inguinal cases were healed within three to six weeks after institution of treatment. The fifth case which was of nine months' duration was cured after sixteen weeks' therapy.

Of the anorectal cases, 11 (39 per cent) were completely healed, the same number markedly improved, 4 improved, and 2 remained unimproved. Fibrous strictures of the rectum were uninfluenced by treatment. There was a higher percentage of cures among the anorectal cases without than with rectal strictures. It is reasonable to consider, however, that the presence of stricture necessitates longer and more vigorous treatment than that given in this study. Rapid healing of the anorectal cases was more likely to occur when treatment was initiated early in the disease.

In the authors' opinion, sulfanilamide is a valuable agent in the treatment of venereal lymphogranuloma.

J. P. GREENHILL.

and appendix. The mass externally resembled the ovary, with a few cystic follicles projecting from the surface. The surface was rough where it had been adherent. On section it showed a large amount of blood clot and at the center a cavity 3.3 by 3 by 1.2 cm., in which there was a well-formed fetus about 1 cm. in length and estimated to be

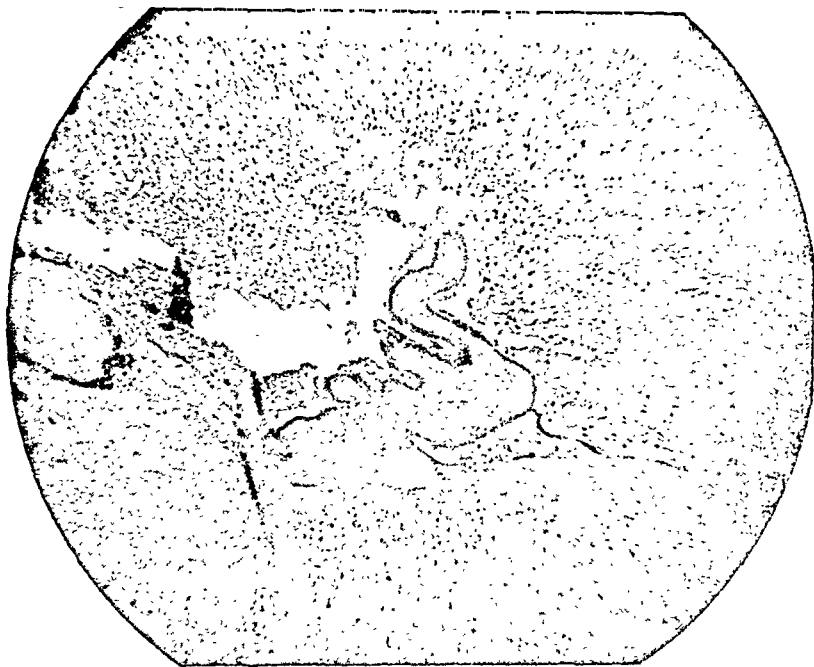


Fig. 1.—Section of ovarian hematoma showing chorionic villi.

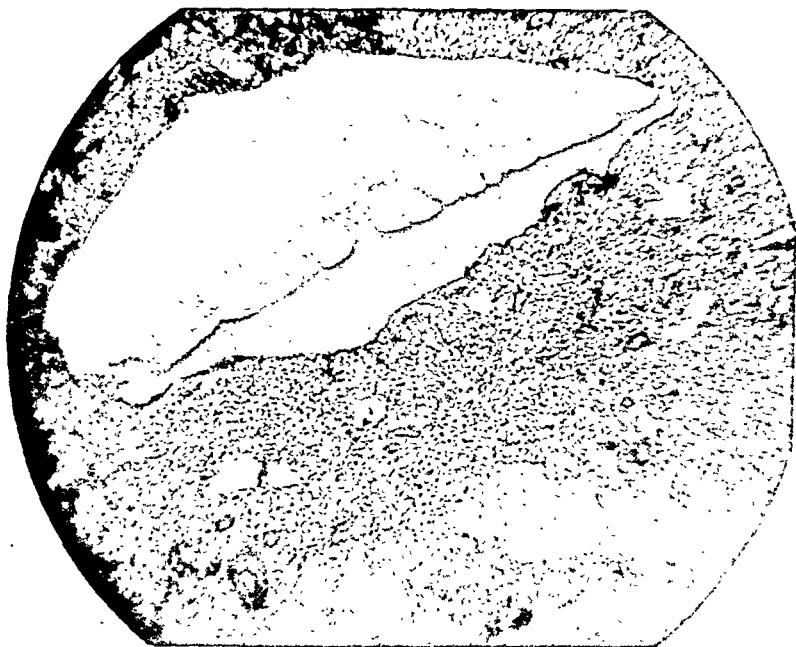


Fig. 2.—Section of wall of ovarian pregnancy showing ovarian stroma; corpus albicans and cystic follicle.

nancy constitute the majority of cases. These lesions, together with other important causes of bleeding are also shown diagrammatically in Fig. 1.

It is our practice to admit to the hospital patients with bleeding in the first trimester of pregnancy. Whether in the hospital or at home, bed rest is essential. A careful history is obtained, particularly with reference to previous interference. Blood is obtained for grouping, white count, and cross-matching, sedimentation rate, hemoglobin and cell volume, particularly if the bleeding has been excessive. A general physical examination is now performed; but vaginal examination is deferred in certain patients, especially those with obvious threatened or incomplete abortion, or infection. If the history suggests ectopic pregnancy,

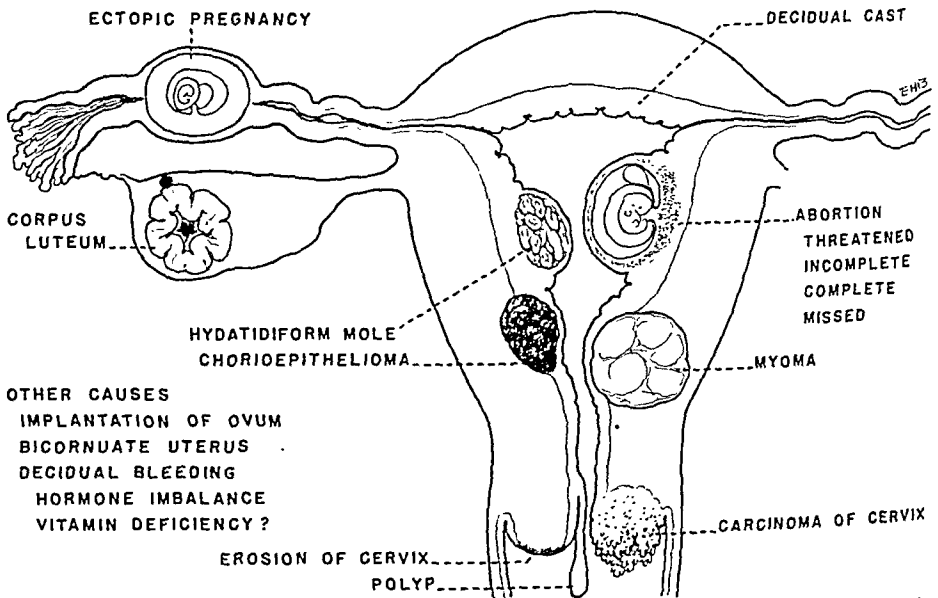


Fig. 1.—Diagrammatic scheme showing sources of ante-partum bleeding causes in first trimester.

vaginal examination is carried out. In other cases, a vaginal culture is taken. The temperature, pulse, and sedimentation rate and white count are observed for twenty-four to forty-eight hours unless excessive bleeding necessitates completion of the abortion.

Interruption of the pregnancy is performed on the basis of continued bleeding. In other patients, the fetus is expelled soon after observation is begun, and in these, operative intervention is often necessary, as shown in Table II. However, the abortion was completed spontaneously in nearly one-third of the cases.

TABLE II. OPERATIVE AND NONOPERATIVE TREATMENT IN INCOMPLETE ABORTION

|                                     |                        |
|-------------------------------------|------------------------|
| Total number of cases               | 1,862                  |
| Spontaneous abortions, no curettage | 602 or 32.3 per cent   |
| Operative completion                | 1,260 or 67.6 per cent |

# Department of Practical Problems in Obstetrics and Gynecology

CONDUCTED BY WILLIAM J. DIECKMANN, M.D.

## TREATMENT OF BLEEDING IN THE FIRST AND THIRD TRIMESTERS OF PREGNANCY

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VAGINAL bleeding in pregnancy must not be regarded as normal. In the first trimester, abortion and ectopic pregnancy are common causes, and require careful differentiation from each other. Bleeding is infrequent in the second trimester, and when it occurs, it is associated with either the causes of bleeding in the first and third trimesters, or with hydatidiform mole. In the third trimester, placenta previa, premature separation of the normally implanted placenta, and partial separation of a low-lying placenta are the main causes of vaginal bleeding.

### BLEEDING IN THE FIRST TRIMESTER

This is of rather frequent occurrence, often requiring hospitalization. Of 24,289 pregnancies on the indoor service, 2,209 patients, or 9.0 per cent, were admitted to our clinic for treatment of bleeding.

The causes of bleeding in this group of patients is shown in Table I. Complete and incomplete abortion, threatened abortion, and ectopic preg-

TABLE I. CAUSES OF BLEEDING IN THE FIRST TRIMESTER OF PREGNANCY INDOOR SERVICE OF THE LYING-IN HOSPITAL, SEPT. 1, 1932, TO DEC. 31, 1940

|  | TOTAL CASES  |
|--|--------------|
| Abortion, complete, or incomplete        | 1,648        |
| Threatened abortion                      | 229          |
| Undetermined                             | 185          |
| Ectopic pregnancy                        | 85           |
| Hydatidiform mole                        | 33           |
| Erosion or polyp                         | 18           |
| Myoma                                    | 5            |
| Chorionepithelioma                       | 4            |
| Carcinoma of cervix                      | 2            |
| Total                                    | 2,209        |
| Total number of pregnancies studied      | 24,289       |
| Incidence of bleeding in first trimester | 9.0 per cent |



patients, or six times the clinic incidence. This supports the view that placenta previa occasionally may be the cause of spontaneous abortion. On the other hand, premature separation of the placenta was not increased in this group of patients.

TABLE III. END RESULTS IN 439 PATIENTS HAVING ANTE-PARTUM BLEEDING IN THE FIRST TRIMESTER

|  | NUMBER | PERCENTAGE | CLINIC CONTROL FIGURE |
|--|--------|------------|-----------------------|
| Abortion   | 69     | 15.7       | 6.8                   |
| Premature delivery   | 29     | 6.6        | 2.7                   |
| Full-term delivery   | 266    | 60.5       | 89.3                  |
| Unknown—did not return, delivery elsewhere, or had induced abortion? | 75     | 17.1       |                       |
| Total  | 439    | 99.9       |                       |
| Other complications:   |        |            |                       |
| Placenta previa  | 13     | 2.9        | 0.52                  |
| Premature separation   | 2      | 0.4        | 0.36                  |
| Infantile mortality  | 18     | 4.1        | 3.5                   |

#### BLEEDING IN THE THIRD TRIMESTER

Ante-partum hemorrhage in the last third of pregnancy is generally due to a partial or complete separation of the placenta from the uterine wall. When the placenta is implanted in the neighborhood of the internal os, we are dealing with the various types of placenta previa—centralis, lateralis or partialis, and marginalis. On the other hand, if the organ occupies its normal site in the upper portion of the uterus and separation occurs, we speak of premature separation of the normally implanted placenta. In addition to these two distinct entities, there is a group, in which diagnosis is often difficult to establish, comprising the cases of partial separation of a lowly implanted placenta. Inspection of the maternal surface of the placenta, immediately after its delivery, will often establish the diagnosis.

TABLE IV. CAUSES OF ANTE-PARTUM BLEEDING IN THE THIRD TRIMESTER OF PREGNANCY (SEPT. 1, 1932, TO DEC. 31, 1941)

|   | CASES         | INCIDENCE PER CENT |
|---|---------------|--------------------|
| Placenta previa   | 134           | 0.52               |
| Premature separation of the normally implanted placenta | 93            | 0.36               |
| Separation of placenta with low implantation            | 334           | 1.3                |
| Undiagnosed placenta previa                             |               |                    |
| Cervical lesions  |               |                    |
| Total   | 561           |                    |
| Total number of term pregnancies                        | 25,531        |                    |
| Incidence of bleeding                                   | 2.19 per cent |                    |

In our cases under discussion, bleeding during the third trimester occurred in 561 of 25,531 pregnancies reaching viability or term, an incidence of 2.19 per cent. A definite diagnosis of placenta previa was

Invasion of the uterus is avoided in febrile patients unless hemorrhage forces the issue. In these, intramuscular pituitrin, at times, has been of value in expression of the products of conception. Certain of these cases have shown the beta hemolytic streptococcus on vaginal culture, and in these chemotherapy has given good results. Recently, we have employed sulfadiazine in the treatment of these patients.

If a diagnosis of extrauterine pregnancy has been made, laparotomy is urgently indicated. Whole blood or plasma must be in readiness in all cases and given as indicated, usually during the laparotomy. Prompt laparotomy and blood transfusion, during and following operation, are the important factors in the treatment of women suffering from ruptured ectopic pregnancy. In a few instances, the patient's condition may be so desperate that transfusion should precede the operative procedure. This treatment, with particular emphasis on blood transfusion and prompt laparotomy, has been followed in our 85 consecutive patients with an extrauterine pregnancy and has resulted in a maternal mortality of 1 in 85, or 1.18 per cent.

Another group of patients with bleeding in the first trimester ceased bleeding after the preliminary twenty-four to forty-eight hours of observation. There were 439 patients in this group, of which 295 went to viability or term. Thus, 67.1 per cent were carried to viability or term, with a fetal mortality of 4.1 per cent. Congenital anomalies were not higher in this group. These patients were treated with bed rest, vitamin E, progesterone, thyroid, and other measures, and for the most part received no specific consideration on which to judge the results. Nevertheless, the end results compare favorably with those who use only progesterone or vitamin E, or some other therapy. This raises a serious question as to the efficacy of specific therapy unless a deficiency has been demonstrated.

Moreover, there are other causes of bleeding, as shown in Table I. For example, cervical erosion and polyp may be the cause of the bleeding, and not a threatened abortion. Naturally in these, specific therapy, using this or that hormone or vitamin will be credited with saving the pregnancy, when bleeding was due to another cause. Therefore, it is our practice to perform a sterile visual inspection of the cervix before the patient is discharged in order to detect other causes for the bleeding. Such examination disclosed carcinoma of the cervix in two cases. These were treated disregarding the pregnancy.

Further end results of our treatment of 439 cases of vaginal bleeding are shown in Table III. As can be seen, over two-thirds of the patients had a premature or full-term delivery. The abortion rate was about twice that of the clinic rate of 6.8 per cent, and premature delivery occurred two times as frequently as in the total clinic population. The fetal mortality was nearly the rate for the clinic. Of significance was the subsequent development of placenta previa in 2.9 per cent of these

TABLE V. COMPARISON OF THE MODE OF DELIVERY IN PLACENTA PREVIA AND PREMATURE SEPARATION OF THE NORMALLY IMPLANTED PLACENTA

|                              | PLACENTA PREVIA<br>PER CENT | PREMATURE SEPARATION<br>PER CENT |
|------------------------------|-----------------------------|----------------------------------|
| Cesarean section             | 43.2                        | 41.9                             |
| Spontaneous delivery         | 16.4                        | 37.6                             |
| Version and extraction       | 15.6                        | 1.0                              |
| Insertion of a bag           | 10.4                        | 1.0                              |
| Breech extraction            | 6.7                         | 9.6                              |
| Forceps and other operations | 6.7                         | 7.4                              |
| Undelivered (died)           | 0.7                         | 1.0                              |

after delivery as was indicated. Packing of the cervical canal with gauze is never employed.

At times, the vaginal examination was not conclusive as to the cause of the bleeding, especially when the cervix is closed. In some of these, a cervical erosion was found on occasion, or a polyp, or a chronic cervicitis. These patients constitute an *undetermined* group, and in whom a low implantation of the placenta may also have been the cause of the bleeding. Patients in this group are sometimes permitted to go home, particularly when placenta previa has been ruled out. These patients often had an uneventful delivery, as shown in Table VI.

TABLE VI. MODE OF DELIVERY IN PATIENTS HAVING ANTE-PARTUM BLEEDING OF UNDETERMINED ORIGIN (COMPARE WITH TABLE V)

|                      | NUMBER | PER CENT |
|----------------------|--------|----------|
| Cesarean section     | 20     | 5.9      |
| Spontaneous delivery | 240    | 71.8     |
| Operative delivery   | 74     | 22.2     |
| Total                | 334    | 99.9     |

The maternal and fetal mortality in ante-partum bleeding in the third trimester are shown in Table VII, and indicate a marked increase when this complication of pregnancy is present. In placenta previa our maternal mortality was 0.75 per cent, and in premature separation of the normally implanted placenta 3.2 per cent.

TABLE VII. TOTAL MATERNAL AND FETAL MORTALITY IN ANTE-PARTUM BLEEDING IN THE THIRD TRIMESTER

| GROUP   | NO. OF<br>CASES | MORTALITY |          |       |          |
|---|-----------------|-----------|----------|-------|----------|
|   |                 | MATERNAL  |          | FETAL |          |
|   |                 | NO.       | PER CENT | NO.   | PER CENT |
| Placenta previa                                 | 134             | 1         | 0.75     | 31    | 23.1     |
| Premature separation                            | 93              | 3         | 3.2      | 49    | 52.6     |
| Separation of placenta with<br>low implantation | 334             | 0         | 0        | 44    | 13.1     |
| Undiagnosed placenta previa                     |                 |           |          |       |          |
| Cervical lesions                                |                 |           |          |       |          |
| Total   | 561             | 4         | 0.71     | 124   | 22.1     |

made in 134 patients and premature separation of the normally implanted placenta in 93, giving an incidence of 0.5 per cent for the former and 0.36 per cent for the latter.

It is our practice to hospitalize every patient with bleeding in the last trimester of pregnancy. Upon admission, blood is obtained for grouping and cross-matching, and a suitable donor or blood in the Blood Bank procured. Hemoglobin and cell volume determinations are, of course, carried out. Thereafter, a careful history is obtained and physical examination made, the pulse and blood pressure being carefully noted. If there is no urgency, due to the patient's general condition or to excessive blood loss, she is observed for four or five days before vaginal examination is performed. If the patient is not at term, a longer period of time may be permitted to elapse. During this period of observation, the bleeding generally ceases, or the patient goes into labor and delivers spontaneously. On the other hand, persistent bleeding may necessitate earlier examination and intervention.

The sterile vaginal examination is performed in the operating room where everything is in readiness for transfusion, laparotomy, or conservative treatment, such as the introduction of a bag. The location of the placenta, the parity, age, and condition of the mother, the condition of the cervix, and the estimated size and condition of the offspring are the main factors to be taken into consideration in the decision as to method of treatment.

It is our practice, in general, to restrict cesarean section to patients with central placenta previa and to those with partial placenta previa with a cervix too rigid to permit easy introduction of a balloon. We place more emphasis on the condition of the cervix than on the degree of partial or incomplete placenta previa. In those patients with partial placenta previa in whom a balloon is used, it is of importance that a large-sized bag be introduced into the amniotic cavity after rupturing the membranes. If a bag is not available, as may happen at home, satisfactory results may be achieved by Braxton Hicks' bipolar version, provided extraction is not attempted before the cervix is fully dilated.

The above conservative and expectant treatment applies primarily to patients with placenta previa or with a placenta of low implantation. In the patient with separation of the normally implanted placenta, severely ill and in shock, immediate interference may be imperative; but, here also, the most important phase of proper treatment consists of the immediate procurement of suitable blood for transfusion.

Operative interference is frequently employed for both placenta previa and premature separation, as shown in Table V. However, certain cases in either group were permitted to deliver spontaneously. In others, a Voorhees bag was inserted, and in others, artificial rupture of the membranes sufficed to hasten delivery. Transfusions were given before and

As shown in Table IX, location of the placenta in the upper and lower portions of the uterus was made on the bulk of the placental shadow in the film. Most of the placentas were located on the anterior or posterior wall of the uterus, with 52 per cent on the anterior wall and

TABLE IX. LOCATION OF THE PLACENTAL SITE IN ROENTGENOGRAMS OF 94 CASES

|                | UPPER UTERUS | LOWER UTERUS | TOTAL |
|----------------|--------------|--------------|-------|
| Anterior wall  | 27           | 22           | 49    |
| Posterior wall | 38           | 2            | 40    |
| Fundus         | 3            | 0            | 3     |
| Lateral walls  | 2            | 0            | 2     |
| Total          | 70           | 24           | 94    |

42 per cent on the posterior wall. In the collective anatomic material of Pinard and Varnier and Van Cauwenberghe, 51 per cent were on the posterior wall and 39 per cent on the anterior wall, and this indicates a reversal in the anatomic percentages when compared with the x-ray findings, as shown in Table X. It is to be recalled that most of our

TABLE X. COMPARISON OF THE PLACENTAL SITE IN RADIOGRAPHIC AND ANATOMIC MATERIAL

|                | PRESENT X-RAY STUDY |          | ANATOMIC MATERIAL OF<br>PINARD AND VARNIER AND<br>VAN CAUWENBERGHE |          |
|----------------|---------------------|----------|--|----------|
|                | NO.                 | PER CENT | NO.  | PER CENT |
| Anterior wall  | 49                  | 52       | 89   | 39       |
| Posterior wall | 40                  | 42       | 116  | 51       |
| Fundus         | 3                   |          | 1  |          |
| Lateral walls  | 2                   |          | 20   |          |
| Total          | 94                  |          | 226  |          |

patients were selected for study because of ante-partum bleeding. It appears from the higher incidence of placental attachment to the anterior wall that bleeding is more prone to occur under such circumstances. This conclusion is supported in part by the fact that in 10 out of 12 cases of placenta previa, the placenta was on the anterior wall.

As so often happens in the course of clinical studies, other findings are made apart from the original scope of the investigation. It was of interest to analyze the mechanism of the third stage in 75 cases having vaginal delivery on whom the placental site had been located in roentgenograms. Previous writers on the subject have not correlated the mechanism of Schultze and Duncan with the placental site. This has been done in Table XI. It can be seen that the Schultze mechanism occurred most frequently when the placenta was situated in the fundus and on the posterior wall. The Duncan mechanism was observed when the placenta was situated on the anterior wall and in the lower uterine segment.

It seems apropos to discuss separation of the placenta in the light of this new evidence. It has been generally conceded that detachment of

It is to be noted that the maternal mortality in all our patients with ante-partum bleeding during the latter part of pregnancy is 0.71 per cent, or 7.1 per 1,000, as compared with the clinic figure of 1.98 per 1,000. The fetal mortality is very markedly increased over the clinic figure, due primarily to the high fetal death rate incident to premature separation of the normally implanted placenta (52.6 per cent). The fetal mortality in placenta previa is 23.1 per cent. This latter figure may be somewhat reduced by the wider use of cesarean section. However, we are opposed to such extension of abdominal delivery, because the majority of the infants are premature and of the added risk to the mother.

In certain patients with vaginal bleeding, a closed cervix prohibits diagnosis of placenta previa. If the patients are a month from term, they are usually kept in the hospital until delivery. This represents an expensive form of treatment which has been justified in terms of a lowered fetal and maternal mortality. However, any procedure which can reduce this expenditure deserves investigation. For this reason, we have employed the x-ray in order to locate the placental site. In a series of 94 patients studied, 71 had antepartum bleeding. The causes of the bleeding in these cases is shown in Table VIII.

TABLE VIII. CAUSES OF ANTE-PARTUM BLEEDING IN 71 CASES STUDIED RADIOGRAPHICALLY

|                                    |    |
|------------------------------------|----|
| Cervicitis                         | 6  |
| Placenta previa                    | 12 |
| Proved by operation or at delivery |    |
| Low implantation                   | 4  |
| Undetermined                       | 49 |
| Total                              | 71 |

Again, it is seen that a large number of patients fall into an undetermined group. However, placenta previa was diagnosed in 12 cases, all of which proved to be correct.

Location of the placental site by x-ray was advocated by Snow and Powell in 1934. About the same time Ude and Uner called attention to the diagnosis of placenta previa using contrast dye in the bladder. Our knowledge of the subject has been augmented by the reports of Snow and Rosensohn and of Brown and Dipple. It is our practice to take a lateral film, and if this fails to disclose the placental site, a frontal film is taken. Location of the placental site is sometimes difficult prior to the seventh month of gestation. In our series of 94 cases, of which 71 had ante-partum bleeding, the placental site was localized in all patients. Brown and Dipple were able to recognize the placenta in 85 per cent of their cases. In several of our cases, the pelvic bones obscured the placenta in the lateral film. In these, frontal films were of value in locating the placenta in the fundus or on the lateral wall.

3. Other causes of bleeding were: (a) ectopic pregnancy, (b) hydatidiform mole, (c) erosion of cervix or polyps, (d) chorionepithelioma, (e) carcinoma of the cervix.

4. The proper treatment for patients with bleeding of the first trimester includes hospitalization, bed rest, blood grouping and matching, and physical examination. Observation for a varying period of time is essential in threatened as well as incomplete abortion. Conservative treatment is recommended in the presence of potential or actual infection of the uterine cavity.

5. Vitamin E and perhaps progesterone are of value in certain cases of threatened abortion. A low basal metabolic rate must be corrected with proper thyroid therapy.

6. Dilatation and curettage are performed on the basis of continued or excessive bleeding in incomplete or threatened abortion. The Aschheim-Zondek test is of value in these cases.

7. Curettage is not performed in infected patients. Hemorrhage in these patients may necessitate evacuation of the uterus with the finger or ovum forceps, used with utmost care.

8. The treatment for ectopic pregnancy is laparotomy with adequate transfusion.

9. Cervical erosion, polyps, and carcinoma of the cervix, although infrequent causes of bleeding, must be ruled out by examination. If these are present, the appropriate therapy is applied. In carcinoma of the cervix, early treatment is essential and must be carried out irrespective of the gestation.

10. Bleeding of the last third of pregnancy is due usually to placenta previa or premature separation of the placenta.

11. The incidence of placenta previa was 0.52 per cent and of premature separation of the normally implanted placenta 0.36 per cent.

12. All patients with bleeding in the latter third of pregnancy must be hospitalized and a suitable donor or blood from a blood bank procured immediately.

13. In all these cases, except those in shock or with excessive bleeding, an observation period of several days is indicated.

14. Our treatment in placenta previa is conservative, including the introduction of a bag in certain cases, except in central placenta previa, or in partial placenta previa with a fairly closed, long, or rigid cervix. In this latter group cesarean section becomes the procedure of choice.

15. In premature separation of the normally implanted placenta, cesarean section is performed unless the cervix is partially dilated and early vaginal delivery may be expected.

16. Where cesarean section is performed for premature separation of the placenta, hysterectomy should be done only in those cases where great disintegration of the muscular wall of the uterus is present and the organ does not contract satisfactorily.

TABLE XI. THE MECHANISM OF LABOR IN THE THIRD STAGE WITH REGARD TO LOCATION OF THE PLACENTAL SITE

|                | SCHULTZE            | DUNCAN              | TOTAL    |
|----------------|---------------------|---------------------|----------|
| Upper uterus   | 43 or 70.5 per cent | 18 or 29.5 per cent | 61 cases |
| Lower uterus   | 2 or 13.6 per cent  | 12 or 86.4 per cent | 14 cases |
| Total          |                     |                     | 75 cases |
| Anterior wall  | 16 or 42.1 per cent | 22 or 57.9 per cent | 38 cases |
| Posterior wall | 28 or 75.9 per cent | 9 or 24.1 per cent  | 37 cases |
| Total          |                     |                     | 75 cases |

the placenta occurs along Nitabuch's layer which acts as a perforated line between the placenta and the decidua vera. Festooning, shortening of the uterine muscle fibers, and contraction of the uterus serve to reduce the size of the placental site. Pinard and Varnier have shown that the uterine wall is thinner at the site of placental attachment. This view is also borne out by the specimens in Canton's *Atlas* and by Morton's specimen of an uterus with placenta previa. It can be assumed that the thicker portion of the uterus can exert greater contraction than the thinner placental site. Under such circumstances, placental separation is probably initiated in the peripheral circumference, spreading rapidly to the center as the musculature over the placental site begins to contract. Contraction of the uterine musculature "ligates" the vessels and sinuses so that the retroplacental hematoma is of very small or almost negligible size, which is a not infrequent clinical finding. This concept receives additional support from the cases of low implantation or marginal placenta previa having partial separation. Bleeding is a frequent phenomenon under such circumstances, probably because the placenta is attached in the noncontractile portion of the uterus.

A word of warning to the general practitioner, as well as to the specialist, may not be out of order. The vaginal pack or tamponade must not be used, because of its inability adequately to control bleeding and the danger of infection, even under the best sterile precautions. In the occasional instance one may be forced to use the vaginal pack, wholly as a temporary expedient to check bleeding sufficiently to allow transportation to a hospital. The manual or instrumental dilatation of the cervix in patients with bleeding near term is to be strongly condemned, because of the inevitable cervical and at times lower-uterine lacerations resulting from such a procedure.

#### SUMMARY

1. Bleeding during the first third of pregnancy occurred in about 10 per cent of all obstetric patients admitted to the New York Lying-in Hospital in the past ten-year period.

2. This bleeding was due mainly to abortion, complete or incomplete, or to threatened abortion.



# Society Transactions

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## NEW YORK OBSTETRICAL SOCIETY

*MEETING OF MARCH 10, 1942*

The following papers were presented:

**Transplantation of Fascia for Relief of Urinary Stress Incontinence.** By Albert H. Aldridge, M.D. (For original article, see page 398.)

**Diffuse Luteinization of the Ovaries Associated With the Masculinization Syndrome.** Joseph A. Gaines, M.D. (by invitation). (For original article, see page 975, June, 1942, issue.)

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## OBSTETRICAL SOCIETY OF PHILADELPHIA

*MEETING OF DECEMBER 4, 1941*

The following papers were presented:

**Adenocarcinoma of the Uterus Followed by Sarcoma.** Dr. Isador Forman.

**Hydatid Mole With a High Persistent Titer of Gonadotropic Hormone.** Dr. Owen J. Toland. (For original article, see page 502.)

**Vulvovaginitis in Childhood.** Dr. Walter Susaman.

**Maternal Syphilis in an Industrial Center.** Dr. Chester Reynolds.

*MEETING OF MARCH 5, 1942*

Papers presented:

**The Histopathologic Diagnosis of the Atypical Endometrium.** Bernard Mann, David R. Meranze (by invitation), and Leib J. Golub. (For original article, see page 460.)

**An Evaluation of the Various Types of Cesarean Section.** Edward A. Schumann.

**Some Nutritional Problems of Surgical Patients.** I. S. Ravdin, (by invitation).

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## OBSTETRICAL SOCIETY OF BOSTON

*MEETING OF JANUARY 20, 1942*

The following case report was given:

**Bilateral Ovarian Dermoid Cysts Complicating Pregnancy Treated by Bilateral Oophorectomy.** Robert H. Goodwin, M.D. (For original article, see page 525.)

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*MEETING OF FEBRUARY 17, 1942*

The following paper was presented (by invitation):

**The Use and Potency of Synthetic Estrogens.** Dr. J. P. Greenhill, Chicago, Ill. (For original article, see page 475.)

17. With the treatment as outlined above our maternal mortality from placenta previa was 0.75 per cent and from premature separation of the placenta 3.2 per cent. The maternal mortality in all patients with antepartum bleeding during the last trimester of pregnancy, including low implantation and undiagnosed placenta previa, was 0.71 per cent.

18. We do not advocate wider use of cesarean section in placenta previa on the basis that it will increase the number of living infants, for cesarean section still carries an appreciable maternal mortality due to infection and hemorrhage.

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**Lazarus and Schiffrin:** An Unusual Case of Benign Multiple Chorionic Villi Implants in Peritoneal Cavity Accompanied by Hemoperitoneum, Ann. Surg. 115: 93, 1942.

The macroscopic appearance of an extrauterine chorionepithelioma is that of a tumor resembling a hematoma, presenting no anatomic relationship to the site of a pre-existing placenta, located anywhere in the peritoneal cavity, portio vaginalis, broad ligament, or in the vagina. The normal chorionic villus differs from the chorionic villus of a chorionepithelioma in that the cells of the latter show a greater tendency to invade blood vessels and to cause vasodilatation of surrounding capillaries. Tumors vary widely in their content of Langhans' cells and syncytium. The sites of predilection of chorionepithelioma are the lungs, vagina, and vulva.

Uterine bleeding is the outstanding symptom of chorionepithelioma, and may appear during or after the termination of pregnancy. The author reports a case of extrauterine chorionic implants found during a laparotomy for acute surgical abdomen. They appeared as dark purplish spots over the surface of the tube and the peritoneum. The villi were benign abdominal implantations. Repeated Aschheim-Zondek tests were negative, and continuous observation of the patient showed her to be perfectly well.

WILLIAM BERMAN.

# Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

## Selected Abstracts

### Menstruation

**Lozner, Taylor and Taylor:** The So-Called Coagulation Defect in Menstrual Blood, *New England J. Med.* 226: 481, 1942.

The fluidity of menstrual blood and its apparent failure to clot have been accepted as established facts with, however, little agreement as to their cause. These phenomena have been variously ascribed to the presence of an anticoagulant, to the absence of one or more factors concerned with blood coagulation and to changes in the circulating blood.

Carefully planned studies of these writers showed that menstrual blood is strikingly similar to defibrinated blood and serum in its behavior toward thrombin, prothrombin, and fibrinogen. These observations indicate that the fluidity of the menstrual blood is caused by the absence both of prothrombin and fibrinogen. This can only mean that the menstrual fluid is blood that has already clotted, and that there is no coagulation defect. Menstrual blood actually is a suspension of the formed elements of blood and tissue debris in serum.

HUGO EHRENFEST.

**Langman, Louis, and Burr, H. S.:** An Electrical Study of the Human Cervix Uteri, *Anat. Rec.* 82: 427, 1942.

Using a microvoltmeter with one lead on the cervix, and the other on the ankle, more than 150 records from 8 women have been taken. In nine cycles the cervix became negative for twenty-four to forty-eight hours. The authors state that this shift is associated with ovulation, although in only one case did it occur on the fourteenth and the fifteenth day.

L. M. HELLMAN.

**Greene, Raymond:** Influence of Menstruation on Suspension Stability of Red Cells, *Lancet* 2: 556, 1941.

The red cell sedimentation rate was measured on every day of the menstrual cycles of 10 healthy women. The figures obtained showed that, contrary to general belief, there is no change in the suspension stability of erythrocytes characteristic of any phase of the cycle.

CARL P. HUBER.

**Sammartino, R., and Herrera, R. G.:** Evidence of the Persistence of the Utero-Ovarian Cycle in Various Gynecopathies, *Rev. méd. latino-am.* 25: 375, 1940.

In a well-illustrated article the authors present sections of ovarian and endometrial material from 100 operative cases. In each case parallel illustrations show the endometrium and the corpus hemorrhagicum or luteum of the current menstrual

## PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY

MEETING OF APRIL 13, 1942

The following papers were presented:

**Pseudomyxoma Peritonei.** Dr. H. W. Erving (by invitation). (For original article, see page 492.)

**Diabetes and Pregnancy.** Dr. L. L. Pennock (by invitation).

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**Ward, George Gray:** Benign Gynecologic Hemorrhages, J. A. M. A. 115: 1625, 1940.

In 19,603 discharges at the Woman's Hospital, New York, severe hemorrhage occurred in 371 cases or nearly 2 per cent. The author reviews the results of the treatment of functional bleeding with such measures as progesterone, chorionic gonadotropin, moccasin snake venom, repeated curettage, radium (200 to 300 mg. hours), and testosterone propionate. He states that 600 mg. hours is within the danger zone of sterilization. In functional bleeding after the menopause, the most satisfactory treatment comprises adequate curettage to rule out possible malignant disease, and the intrauterine application of radium. A dose of 1,800 mg. hours radiation is an average amount to insure permanent stopping of the bleeding. The author prefers this to x-rays.

Myomas that do not invade or encroach upon the endometrium are not the cause of uterine bleeding. The bleeding in nonmyomatous and in myomatous uteri is identical in origin and it is hormonal. Bleeding from a fibroid uterus after the menopause is always to be considered of importance. It may arise from a necrotic submucous growth, sarcoma, or carcinoma. The author advocates surgical therapy as a general rule in bleeding myomatous uteri. During the childbearing age, conservative therapy is the treatment of choice. In the fifth decade irradiation is excellent for abnormal bleeding with associated small intramural growths. Radium is of no value in the postclimacteric fibroid with no bleeding. The author advises surgical treatment of adenomyosis. The most common cause of intra-abdominal hemorrhage is a ruptured ectopic pregnancy. Massive abdominal hemorrhage may result from a ruptured corpus luteum cyst. Among less frequent causes of vaginal bleeding are mentioned cervical erosions, senile vaginitis, hypertension, typhoid, pneumonia, chronic valvular disease, diabetes, hemophilia, scurvy, and syphilis.

WILLIAM BERMAN.

function in the primary genital tissues themselves. This demands tissue study of endometrium and vaginal mucosa. Only the latter, in the young girl, is more readily available for investigation through aspiration of vaginal desquamation discharge.

Endocrinologists have hoped to find a cure for dysmenorrheas. "None of the honest endocrinologists that I know about think they have anything like the answer to the dysmenorrhea question."

For the treatment of delayed or incomplete development of adolescence or of different aspects of hypogonadism estrogenic substances should not be used. They never stimulate development of the ovaries but in large doses, used for a long time, actually inhibit anterior pituitary activity and thus reduce ovarian function. We should want to employ gonadotropic anterior pituitary material but that commercially available for the last decade is far from satisfactory. Chorionic gonadotropin, extracted from the relatively cheap source of pregnancy urine, stimulates the ovaries of rabbits and rats but not those of the human female. Gonadotropic preparations from the serum of pregnant mares only recently have become available. They actually stimulate human ovaries. Improvement is being made in such preparations, but we still are in the stage of earliest and rather unsatisfactory development. "However our patients will not wait."

Thyroid has been overworked. It is really useful only if thyroid underfunction can be definitely established. In younger girls this cannot be done by means of the basal metabolic test. "If the serum cholesterol concentration is significantly increased, we have very good reason to suspect hypothyroidism." In jittery adolescent girls, thyroid may easily aggravate their nervousness. "Certainly the use of thyroid on an obese child who is not a hypothyroid is wasted."

"Precocious adolescence always appeals to me as a sort of tragedy, psychologically and sociologically." Most of these cases, contrary to prevailing views, are not connected with tumors of any structure, "but are due to increased activity of some of the normal mechanisms which bring on adolescence, presumably the anterior pituitary." Only with evidence of beginning adolescence with ages between two and four, maybe up to ten years, search for some beginning newgrowth should be made.

HUGO EHRENFEST.

Klingelhöfer, W.: Subsequent Fate of Girls With Juvenile Bleeding, Zentralbl. f. Gynäk. 65: 743, 1941.

In the treatment of juvenile bleeding, the influence of extragenital disease, anatomic variations, polyps and avitaminosis must be considered. Most cases, however, have an associated disturbance of ovarian function. The author was interested in the subsequent fertility of these patients and found 15 women whom he could study after their climacteric.

All but 3 patients had no further signs of ovarian insufficiency after entering the third decade of life. None had attempted to prevent pregnancy, but of the group 4 were sterile, 1 had aborted, 3 had 1 living child without further pregnancies, 6 had 1 living child plus 1 or more abortions. Only 1 had more than 1 living child. The author concludes that the productivity of women having suffered from juvenile bleeding is subnormal.

R. J. WEISSMAN.

Vöge, A.: Therapy of Hemorrhage in Puberty, Zentralbl. f. Gynäk. 65: 254, 1941.

Vöge successfully treated 3 cases of juvenile glandular cystic hyperplasia of the endometrium by directing his efforts at producing a secretory mucosa. He administered gonadotropic hormone intravenously with the intention of converting per-

cycle. The authors wish to show that despite the presence of pelvic pathology of many types, the cyclic activity of the uterus and of the ovary proceeds pretty much on schedule, unless the pathology present is extensive or destructive.

R. J. WEISSMAN.

**Nobecourt, Pierre:** *The Relationships Between the First Menstruation and the Clinical Onset of Tuberculosis*, Presse méd., No. 48, 929, 1940.

The author compares the time of onset of menses between a group of nontuberculous girls and a group of tuberculous girls. There were 811 patients, aged 10 to 18 years, in the nontuberculous group. Among this group, 422 girls (52 per cent) had passed their menarche. The average age at the time of the appearance of the first period, in this group, was 13 years and 3 months.

There were 103 girls, aged 10 to 17 years, in the tuberculous group and 51 (49 per cent) had reported their menarche. The average age at the time of the first period, in the tuberculous group, was 13 years.

The author reports that the beginning of clinical tuberculosis among the 103 cases was: before the first menses in 33.3 per cent, following the menarche in 58.8 per cent, and simultaneous with the first menstruation in 7.8 per cent of the cases.

The percentage of positive skin tests took its first great increase during the fourteenth year and was followed by a slight increase over this finding during the fifteenth year.

The author concludes that one cannot generalize on the basis of statistical studies. Early menstruation does not necessarily imply susceptibility to tuberculosis. Rather other factors, such as hygiene, the rate of body growth, and environment, during this period of life furnish the background for the tuberculosis than does any relationship to the precocity of menstruation.

CLAIR E. FOLSOME.

**Sevringhaus, E. L.:** *Menstrual Abnormalities of Adolescence*, J. Pediat. 19: 319, 1941.

Adolescence is not a sudden event but a state of progressive development, continuing not always at the same rate of progress. Maturity in reproductive capacity is not evident until the second decade of life. In recording the state of development of the adolescent usually too much attention is given to obesity and weight which are relatively slightly influenced by gonadal hormones. The latter more definitely influence skeletal structure. Family history must be taken into account because growth and development tend to follow certain family and individual patterns.

Reduced gonadal function manifests itself in different ways and may, but not necessarily does, express itself in delayed menarche for which there are various other causes. The clinical pictures of hypogonadism and hypopituitarism are different but "increasingly we doubt that they are different diagnostic classifications. They merely are different aspects of the same type of thing." These different pictures vary from amenorrhea to menorrhagia, and in between lie wide variations in menstrual intervals and duration of flows. All these manifestations the author now considers as evidence of ovarian underactivity, if they are due to any endocrine disturbance whatever, though menorrhagia or frequent flows still are considered by some as results of overfunction.

Biologic assays, if not done by an adequate laboratory, are worthless; they are of no value to the practicing physician at the present state of methods of study. Failure of complete development of secondary physical characteristics points to an endocrine background but diagnosis depends upon unmistakable evidence of under-

treatment affects beneficially the internal secretion, not only of the ovaries but of the other endocrine glands.

J. P. GREENHILL.

**Bennett, Michael J., and Russell, P. B., Jr.:** Surgical Correction of Oligomenorrhea, Menorrhagia and Menopause by Ovarian Isoplastism, *South. Surgeon* 10: 154, 1941.

This report describes a method whereby certain contrasting types of ovarian dysfunction which have not responded to medication may be corrected by an exchange of ovarian grafts. In the first such corrective procedure which was performed in 1935, the results were successful; subtotal unilateral ovarian grafts were exchanged in two sisters who suffered, respectively, from menorrhagia and amenorrhea of functional origin. Upon the basis of the analysis of numerous case histories, and a correlated histologic study of tissues from the female generative tract, an anatomicoclinical classification was evolved. This was employed to serve as an aid in grouping patients. The two principal categories are: (1) Hyperinterstitial (hypofollicular), and (2) hypointerstitial (hyperfollicular). Complete study of the patients included blood chemistry determinations, biologic assays, and vaginal smears.

Three precautions must be observed preliminary to the performance of ovarian isograft: (1) The patients must be of the same blood group and cross-match satisfactorily; (2) the ovarian dysfunction must be complementary and of the same degree; (3) the tissues must be free of any transferable disease. The technique requires that the ovaries in both patients be simultaneously resected at the hilum with no attempts to secure hemostasis, and immersed in warm physiologic saline solution during the transfer. Coaptation of the transplant is accomplished by continuous suture with an atraumatic needle and No. 00 chromic catgut.

Eighty isoplastics have been performed with a negligible percentage of failure (0.8 per cent uncorrected), and with no deaths as a result of the procedure. The data of 40 of these cases are summarized in this paper. In no instance was supplementary hormone therapy required. Daily pre- and postoperative vaginal smears served to check objectively the results of this operative procedure. A viable graft was visualized at a cesarean section performed ten months later.

ARNOLD GOLDBERGER.

**Siebke, H.:** Menstruation Following Transplantation of Curettage Material in an Endometrium-Free Uterus, *Zentralbl. f. Gynäk.* 65: 1034, 1941.

The author refers to the work of other writers on operative attempts at inducing menstruation. A 32-year-old woman had caustic applications to the uterus three weeks post partum followed by six years of amenorrhea. Uterus and adnexa were normal to palpation, but the uterine cavity was found obliterated. The author curetted the patient's sister. On the fourteenth day of her cycle, and while preparing the patient's womb by reopening the cavity, he carefully planted into it bits of endometrium. Ten milligrams proluton were given at operation and daily for one week. Progynon, 50,000 I.U., was given on alternate days after operation for 6 doses. Morphine, 0.01 Gm., was given to minimize contractions. Eleven days after operation, corresponding to the twenty-fifth day of the donor's cycle, mild bleeding occurred. Seven normal menses had occurred up to the time of writing. Stilbene was given to heighten proliferative activity prior to the third period.

R. J. WEISSMAN.

sistent follicles into corpora lutea. Subsequent curettings showed that one of the girls had an anovulatory cycle although all menstruated in a normal manner following the treatment.

R. J. WEISSMAN.

Pallos, K., and Treite, P.: *The Pathology of Functional Uterine Bleeding in the Climacterium and Post Climacterium*, *Ztschr. f. Geburtsh. u. Gynäk.* 122: 28, 1941.

This report presents a study of Robert Meyer's material from the Institute of Pathology of the First Frauenklinik in Berlin. The endometria were obtained because of uterine bleeding; 509 were from women 42 to 45 years old and included 8 carcinomas of the body of the uterus; 1,243 endometria were from women from 45 years of age to the menopause and included 32 endometrial carcinomas; 38 endometria were taken one-half to two years after the menopause and of these, 17 showed hyperplasia, 8 showed atrophy of the endometrium and 8 carcinoma of the body of the uterus. Of those which were taken more than two years after the menopause, 28 were diagnosed as hyperplasia, 84 as atrophy, and 96 as carcinoma of the body.

The so-called functional bleedings are then discussed at length (40 pages) with many photomicrographs included. Fifty per cent of the cases of functional bleeding during the preclimacterium showed irregular proliferation. In many others there was localized circumscribed hyperplasia. Of those endometria which showed functional (secretory) phase changes, 10 per cent were diagnosed as functional hypertrophy and in association with these, the author describes persistent corpora lutea or theca lutein cysts.

One hundred fifty-six endometria were obtained during menstruation and presumably because of abnormal bleeding. These are divided into the two groups: those from women of 42 to 45 years of age and 45 years of age to the menopause. These showed for the two groups, respectively, normal shedding in 9.6 per cent and 21.8 per cent, prolonged shedding 7.7 per cent and 16 per cent, and irregular shedding 15.4, and 29.5 per cent of the total 156 specimens.

No functioning (secretory phase) endometrium was found more than two years after the menopause and only four times in the period from one-half to two years after the menopause. It is concluded that a hyperplasia occurring naturally more than six years after the menopause justifies the diagnosis of an estrogen producing ovarian tumor.

Partial function (secretory phase) was found not infrequently in endometria showing hyperplasia. The author looks on this as evidence of the presence of a new corpus luteum formation occurring after prolonged hyperplasia.

The report includes much detailed clinical and histologic description of those more recently recognized endometrial disturbances. Too little attention has been given to these in this country and reading this report in the original is well worth while.

J. L. McKELVEY.

Pignoli, Renato: *Capillary Fragility in the Meno-Metrorrhagias and Its Changes Following Tréatment With Ascorbic Acid*, *Ginecologia* 7: 85, 1941.

In 56 patients with menometrorrhagia and 15 women with normal menstrual cycles the author first ascertained the capillary resistance with special techniques.

All these women received an intravenous dosage of 200 mg. of ascorbic acid. Twenty-four hours later repeat fragility studies showed that the capillary resistance remained at a linear level throughout most of the phases of the men-



perhaps by other pathologists as well, and since this will involve correspondence between men scattered in different sections of the country, it will be understood that such reports of findings cannot be made with great promptness.

Finally, the Committee fully appreciates that many of the ovarian tumors submitted to it will be worthy of report by the referring physicians, and it need scarcely emphasize that neither the Committee as a whole, nor any individual member thereof, will utilize any submitted case for publication without the express permission of the referring physician. It is hoped that, as the work progresses, reports of the Committee's studies will be published from time to time, but those referring cases for study will be given full credit in any such publication.

The Committee feels that it has been given a great opportunity to render a worth-while service and it sincerely hopes that individual clinicians and pathologists in all sections of the country will feel that they too can contribute vitally in this project, by developing the routine of sending slides of interesting ovarian tumors, with the above indicated data, to the committee for study and registry. This material should be mailed to Dr. Emil Novak, Laboratory of Gynecological Pathology, Johns Hopkins Hospital, Baltimore, Md.

EMIL NOVAK, CHAIRMAN  
ROBERT MEYER  
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## Item

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### American Board of Obstetrics and Gynecology

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Saturday, February 13, 1943, at 2 P.M. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination held later in the year. All applications must be in the office of the Secretary by November 16, 1942.

Effective this year there will be only one general classification of candidates, all now being required to have been out of medical school not less than eight years, having in that time completed an approved one year general rotating internship and at least three years of approved special formal training, or its equivalent, in the seven years following the interne year. This Board's requirements for internships and special training are similar to those of the American Medical Association since the Board and the A. M. A. are at present cooperating in a survey of acceptable institutions. All candidates must be full citizens of the United States or Canada before being eligible for admission to examinations.

All candidates will be required to take the Part I examination, which consists of a written examination and the submission of twenty-five (25) case history abstracts, and the Part II examination (oral-clinical and pathology examination). The Part I examination will be arranged so that the candidate may take it at or near his place of residence, while the Part II examination will be held late in May, 1943, in that city nearest to the largest group of applicants. Time and place of this latter will be announced later.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

# Announcement

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## A Registry of Ovarian Tumors

At its recent annual meeting the American Gynecological Society undertook the sponsorship of an *American Registry of Ovarian Tumors*, and appointed from its Fellows a committee of five gynecologic pathologists to carry on this work.

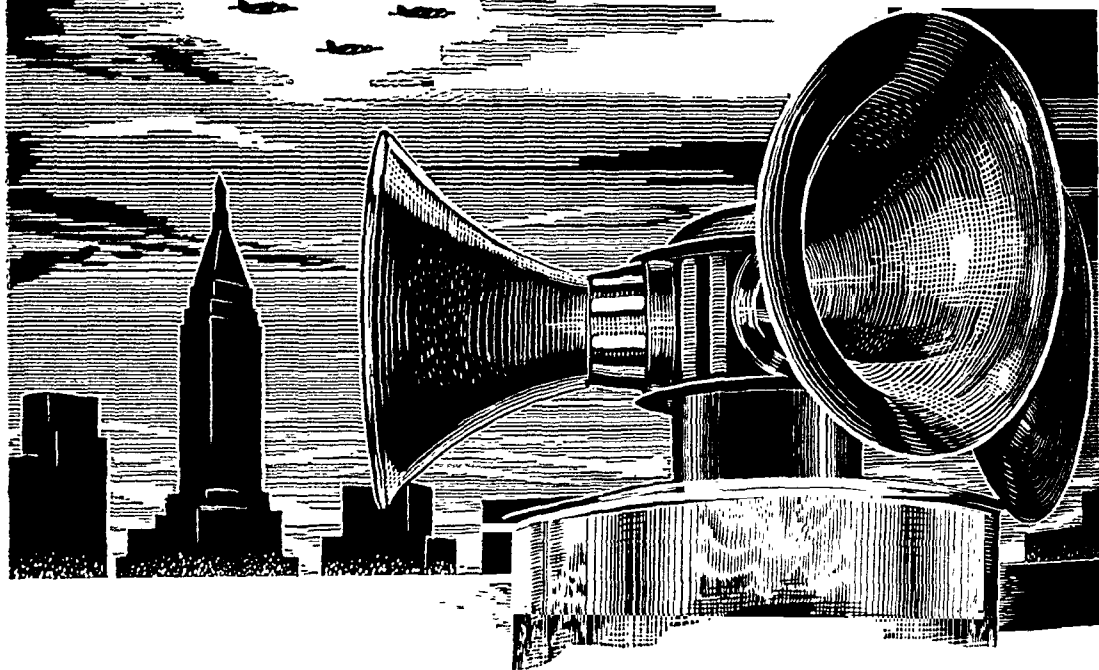
The need and wisdom of such a project must be obvious to every gynecologist, for no problem of pathology is in greater need of clarification. No entirely satisfactory classification of ovarian tumors exists, largely because of our ignorance of the histogenesis of many of these growths. Even in tumor types which are fairly well defined, such as the papillary growths, prognosis is often difficult, because of the not infrequent lack of parallelism between clinical and histologic malignancy, and mistakes in both diagnosis and prognosis are frequent. Again, tumors are not infrequently encountered concerning the nature of which even expert pathologists cannot be certain. Finally, a whole group of ovarian tumors of rather special histogenesis and histology has been described in recent years, and there are many pathologists who, because of the relative rarity of these tumors, have had no opportunity of familiarizing themselves with their histologic characteristics.

Instead of limiting its study to a registry of rare ovarian tumors, comparable perhaps to that which has been employed so successfully by general pathologists with bone sarcoma, the committee has decided to widen its scope to include ovarian tumors of all varieties. It therefore seeks the cooperation of all gynecologists and pathologists in this ambitious project, and appeals to them for cooperation by seeing to it that properly prepared slides of all ovarian tumors, more particularly those of unusual or doubtful nature, be sent to this central registry for composite study by the members of the committee.

With the slides should be sent an adequate clinical history, including such essential data as the patient's age, menstrual and marital history, gynecologic findings, and the operative procedure carried out, as well as a gross description of the tumor. Where photographs of the latter are available, they would be welcome. If the gross specimen or blocks of tissue are sent, they should be fixed in 10 per cent formalin.

It is obvious that the real value of such a study would be enormously lessened if it did not include also a study of the subsequent course of the patients, particularly in the malignant and doubtful groups of tumors. Such correlated clinical and histologic study must be the chief hope of improving our evaluation and classification of ovarian neoplasms. To facilitate such a follow-up study the name of the attending surgeon should be included in the data.

The Committee has no intention of making this a purely diagnostic service, but all those who send in slides will in due course receive reports of the diagnosis and classification arrived at by the Committee. Since each slide will be studied by every member of the Committee, and



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TABLE OF CONTENTS ON PAGE 6

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## CONTENTS FOR OCTOBER, 1942

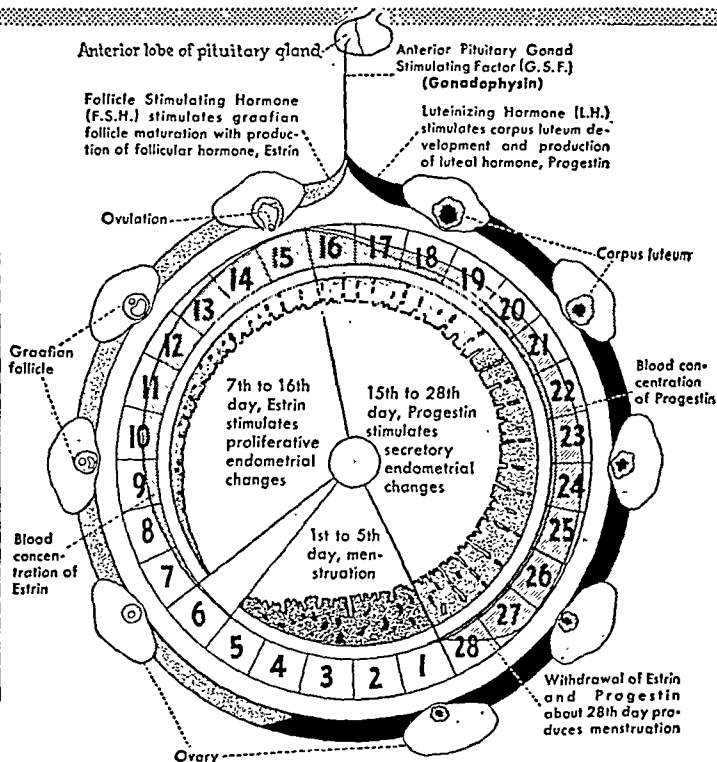
### South Atlantic Association of Obstetricians and Gynecologists Fifth Annual Meeting, February 6 and 7, 1942

|   |     |
|---|-----|
| Utopian Obstetrics. R. A. Bartholomew, M.D., Atlanta, Ga. ....  | 553 |
| Detailed Technique of a Modified Local Anesthesia for Cesarean Section. Alfred C. Beck, M.D., Brooklyn, N. Y. ....  | 558 |
| The Etiologic and Pathologic Factors in a Series of 1,741 Fibromyomas of the Uterus. Richard Torpin, M.D., Edgar Pund, M.D., and W. J. Peeples, B.S., Augusta, Ga. ....   | 569 |
| Eclampsia and Ovarian Pregnancy. C. B. Pride, M.D., Morgantown, W. Va., and M. Pierce Rucker, M.D., Richmond, Va. ....  | 575 |
| Puerperal Uterine Contractions. William Bickers, M.D., Richmond, Va. ....   | 581 |
| Comparative Measurements of the Female Pelvis. Kenneth Dickinson, M.D., and Ivan M. Procter, M.D., F.A.C.S., Raleigh, N. C. ....  | 585 |
| Placental Polyp With Severe Late Puerperal Hemorrhage. Charles W. Dorsey, M.D., Roanoke, Va. ....   | 591 |
| Anencephalus (With Acute Hydramnios) Diagnosed by X-Ray. Waverly R. Payne, M.D., F.A.C.S., and Harvey G. Bland, M.D., Newport News, Va. ....  | 593 |
|   |     |
| Changes in the Female Genital Tract During the Puerperium Induced by Sex Hormone Therapy. Robert N. Rutherford, M.D., Seattle, Wash. ....   | 595 |
| Clinical Experiments in Relation to the Excretion of the Estrogens. II. Functional Flowing. Urinary Estrogens Before, During, and After Progesterone, Estriol, and Cyclic Administration of Progesterone and Estradiol Benzoate. George Van S. Smith, M.D., O. Watkins Smith, Ph.D., and Sara Schiller, B.S., Brookline, Mass. .... | 606 |
| Glomerular Filtration and Renal Blood Flow in the Hypertensive Woman and in Posttoxic Hypertension. C. E. Robinson, M.D., L. V. Dill, M.D., J. F. Cadden, M.A., and C. E. Isenhour, M.A., New York, N. Y. ....  | 616 |
| Posterior Rotation of the Occiput During Labor. Paul Klingensmith, M.D., Philadelphia, Pa. ....   | 623 |
| Spontaneous Abortion and Its Treatment With Progesterone. Lyman W. Mason, M.D., Denver, Colo. ....  | 630 |
| Uses and Abuses of Radiation Therapy in Obstetrics and Gynecology. Herbert F. Traut, M.D., New York, N. Y. ....   | 638 |
| Nutrition Study in Pregnancy. Philip F. Williams, M.D., and Florence G. Fralin, B.S., Philadelphia, Pa. ....  | 647 |
| Postmenopausal Endometriosis. Irving L. Frank, M.D., Philadelphia, Pa., and Samuel H. Geist, M.D., New York, N. Y. ....   | 652 |
| Sexual Libido in the Female. Robert B. Greenblatt, M.D., Frank Mortara, M.D., and Richard Torpin, M.D., Augusta, Ga. ....   | 658 |
| Scopolamine in Obstetrics. Harry M. Kirschbaum, M.D., Detroit, Mich. ....   | 664 |
| The Electroencephalogram in Pregnancy. Frederic A. Gibbs, M.D., and Duncan E. Reid, M.D., Boston, Mass. ....  | 672 |
| Convulsions Following the Intravenous Administration of Pituitary Extract. Charles L. Sullivan, M.D., and Roy J. Heffernan, M.D., F.A.C.S., Boston, Mass. ....  | 675 |

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## CONTENTS (Continued from page 6)

|   |     |
|---|-----|
| The Treatment of Pelvic Inflammatory Disease With Intradermal Administration of Bacillus Coli Vaccine. Earl G. Krieg, M.D., Detroit, Mich. ....             | 681 |
| Estrogen-Withdrawal Bleeding. S. D. Soule, M.D., F.A.C.S., St. Louis, Mo. ....  | 684 |
| Variations in the Electroencephalogram During the Menstrual Cycle. Dorothea Dusser de Barenne, and Frederic A. Gibbs, M.D., Boston, Mass. ....              | 687 |
| The Colostrum Test for Pregnancy in a Prenatal Clinic. Michael Pulver, B.S., M.D., and Lewis B. Posner, B.C.S., B.S., M.D., New York, N. Y. ....            | 690 |
| Uterine Tonus During Labor. Douglas P. Murphy, M.D., Philadelphia, Pa. ....   | 694 |
| Pregnancy and Labor in a Patient With Cardiac Anomaly, Probable Tetralogy of Fallot. Sidney Scherlis, M.D., and Lewis R. Soloway, M.D., Baltimore, Md. .... | 697 |
| Artificial Pyrexia in Four Pregnant Women. William F. Mengert, M.D., and William D. Paul, M.D., Iowa City, Iowa ....  | 702 |
| Portes Cesarean Section. John L. Keyes, M.D., and A. J. Whitehouse, M.D., F.A.C.S., Lexington, Ky. ....   | 705 |
| Allergic Shock Caused by Synapoidin. E. W. Phillips, M.D., Phoenix, Ariz. ....  | 706 |
| A Rare Connective Tissue Tumor (Myxosarcoma) in the Area of the Bartholin Gland. Irving Smiley, M.D., and J. Irving Kushner, M.D., New York, N. Y. ....     | 709 |
| Ante-Partum Rupture of the Umbilical Vein. Wynne M. Silbernagel, M.D., and Roswell S. Fidler, M.D., Columbus, Ohio ....                                     | 712 |
| <b>Department of Practical Problems in Obstetrics and Gynecology</b>  |     |
| Treatment of Heart Disease in Pregnancy. H. J. Stander, M.D., New York, N. Y. ....  | 714 |
| <b>Department of Statistics</b>   |     |
| A Statistical Study of 500 Consecutive Abdominal Hysterectomies. William H. Vogt, Jr., A.B., M.D., and Eugene G. Hamilton, M.D., St. Louis, Mo. ....        | 723 |
| <b>Correspondence</b>   |     |
| Correspondence .....  | 730 |
| <b>Editorial</b>  |     |
| Women in the War Effort .....   | 732 |
| <b>Society Transactions</b>   |     |
| South Atlantic Association of Obstetricians and Gynecologists, Annual Meeting at Atlanta, Ga., February 6 and 7, 1942 .....                                 | 734 |
| <b>Department of Reviews and Abstracts</b>  |     |
| Selected Abstracts—Placenta .....   | 735 |
| Item—American Board of Obstetrics and Gynecology .....  | 740 |
| <b>Roster</b>   |     |
| Roster of American Obstetrical and Gynecological Societies .....  | 741 |
| Books Received .....  | 742 |

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due partly to greater strain and responsibility, irregular rest and eating habits, and greater physical, mental, and emotional hazards. To counteract these tendencies and possible influences, emphasis is put on moderation, equanimity, and the conservation of energy through the middle and later decades of life.

Falk emphasizes that the only compensation for normal fatigue is rest and that it is more important to get an adequate consecutive number of hours' rest than a number of irregular periods of rest. The doctor should not only have ample vacation periods, but also brief periods of complete physical and mental relaxation from the pressure of daily routine. He speculates on just what influence the replacement of man's former necessity for walking may be having on the increase in coronary disease.

Considering the long and expensive years of preparation for the practice of medicine and the fact that the physician has, through years of experience, attained his maximum efficiency and usefulness at the age when coronary disease takes its greatest toll, it is a matter of local and national concern that the public, if for no other reason than its own interest, should modify its time-honored concept of the busy doctor's daily life in order that some of these predisposing causes of coronary disease may be removed.

It would be of interest if the statistics gathered by Falk could be broken down still further to determine which of the specialties in medicine most favored the development of coronary disease. The specialty of obstetrics permits, least of all, avoidance of the factors which predispose to this disease. It is said that one of the most important attributes of the obstetrician should be equanimity, and rightly so, when one considers the need of a calm demeanor to counteract the fears of the patient's family and friends. Whatever benefit equanimity may be to the obstetrician, it would seem to be more than offset by the detrimental effect of many influences peculiar to this specialty.

Nature intended that man should get adequate hours of sleep and rest to remove waste products, repair tissue damage, and restore vitality. The necessity for this is recognized, and in practically all vocations, provision is made to insure that hours of labor shall not interfere with this fundamental need.

How goes it with the obstetrician? For some peculiar reason the majority of labor cases gets under way between the hours of bedtime and daylight and if accommodating enough to begin during the day, seldom fails to delay the hour of retiring. If he has been fortunate to have obtained full rest the preceding night, he is not only able but willing to lose sleep and spare no effort to render ideal service. However, the following day's office and outside work lack something of the necessary efficiency due to loss of sleep. The onset of another labor ruins the expectation of hoped-for sleep the following night. To obtain much-needed rest, he must depend on the less mature judgment

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## UTOPIAN OBSTETRICS\*

A PLAN PROMOTING EFFICIENCY TO THE OBSTETRICIAN AND SERVICE TO  
THE PATIENT

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**I**T happens to be our peculiar lot to live in an age of which there has been none other of equal importance to man's welfare. To win the war and preserve our way of life overshadows every other consideration; yet, no one doubts that another all-out effort will be necessary to win the peace.

In this hoped for period of reconstruction, it is my belief that something should be done to bring to the average physician, and the obstetrician in particular, a more deserved participation in a more abundant life.

There is deep significance behind the facts brought out by Falk in a recent paper entitled "Coronary Sclerosis, the Doctor's Disease."<sup>1</sup> From a study of statistics, he found that coronary disease killed doctors twice as often as laymen. While coronary deaths have increased 114 per cent among all men over a seven-year period, they have increased 240 per cent among physicians. There has been a 50 per cent increase in cardiac deaths among physicians between 1930 and 1940, but, contrasted with this increase from general cardiac causes, is an apparent 600 per cent increase in coronary types.

One cannot explain away these figures simply on the basis of greater diagnostic acumen. The increased susceptibility of the doctor may be

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

overwork but it seems unwise to overstep what the laity regard as reasonable remuneration even for a specialist. Furthermore the obstetrician owes it to himself to retain a sufficient volume of practice to insure wide experience and safeguard himself against periods of economic depression.

It seems to us the solution lies in forming a group, the nucleus of which should be one or two men who control a considerable volume of work. An association of four men in a populous center lends itself to a convenient division of labor. Among the basic requirements there should be congeniality, a spirit of "give and take" flexible enough to smooth over differences of opinion, frankness, honesty, and a willingness to sacrifice some degree of independence and possibly some individual income for the larger benefits to be obtained through such an association. Through free expression of opinion, a standardization of procedure will gradually be evolved. It is essential that the group work exclusively in one institution and that the offices be in or adjacent to the hospital and be easily accessible.

In arranging a rotation of hours, provision must be made for (1) office hours, (2) hospital work, (3) outside work, and (4) definite hours for sleep and recreation.

During the morning hours, two of the group work at the office; the third member remains in the hospital supervising labors, and making rounds, while the fourth member attends to outside work, whether this be teaching, clinics, home calls, or emergencies, but with more or less of the time free for personal use. In the afternoon the two members at the office shift to hospital and outside work, respectively, while the two previously attending to these duties, shift to the office.

At night, one member remains available at the hospital for labor cases until 1:00 A.M.; he is then relieved by another who remains on duty until the day shift begins. This insures considerable rest for these two members. Since outside calls and emergencies are relatively less at night, the other two members are able to use this time for rest or other purposes with little chance of interference. All telephone calls from patients at night are taken by the member on duty at the hospital.

The shifts vary from day to day and week to week. It is possible for the members to have more free time at week ends, since shifts of hours then apply only to duty at the hospital and responsibility for outside calls or emergencies. It is also possible to cover the work with three men, permitting one member of the group to be absent several days to a week each month for recreation or visiting other clinics in search of improved methods.

From the patient's standpoint, what objections may be raised to this manner of obstetric practice? First and foremost, the patient may feel she cannot exercise the privilege of calling upon the physician of her choice. This will be obviated by the fact that during the prenatal period she will contact each member of the group sufficiently often to feel well acquainted with and have confidence in each one of them. If unusual complications arise during pregnancy or labor, she may still designate

of an interne or nurse to supervise progress and determine the ideal time for sedation or interference. If the case extends on into the day, office hours and outside work are disrupted. Cancelled office visits may involve failure to recognize developing toxemia or perform a necessary external version, which are equally as important as the labor, although not so recognized by the patient or family. Cancellation of prenatal visits and postponement of office work entail much inconvenience and waiting to the patients. Should a third successive night's sleep be lost, this patient not only receives inferior service in labor, but the office work receives inferior attention.

Loss of sleep and excessive tiring lower the physician's resistance, increasing his susceptibility to disease and infection. Vacations are too easily postponed. The post-partum patient, coming for her final examination, is over-solicitous concerning her physician's need of a vacation, but the prenatal patient is equally insistent that he be available at the expected date of confinement.

There is need of some practical workable compromise between the laity's concept of an obstetric attendant who must be available, not only around the clock, but also around the calendar, and a plan of obstetric care which will assure the obstetrician definite hours of sleep, recreation, and regular vacations.

Such a plan had been devised and was about to be put into operation by several of us when the present requirements of national defense necessitated postponement, through loss of personnel. For the purposes of this presentation it is unfortunate that we are therefore unable to actually state our experience with what we choose to call "Utopian Obstetrics," but the plan is to be put into effect at the earliest opportunity.

One may appreciate better the fundamental requirements of such an organization if he will trace the evolution of a growing obstetric practice. To paraphrase a Biblical narration: The seven years of famine are succeeded by the seven years of plenty, after which further increase in work causes the obstetrician to ask himself why he ever aspired to a busy obstetric practice anyway. He takes unto himself an associate, who, because he is made of the right stuff, is before long in the same predicament.

We now have an association of two specialists, neither of whom is getting sufficient sleep, recreation, or vacation, nor is the one physically able to take over for the other in respect to office work or any of the above-mentioned necessities. Each one lives in constant fear that the other may be disabled by sickness or accident, and realizes, only too well, the physical impossibility of taking over the additional practice.

It is admitted that in less populous areas, the problem may not be such a pressing one, but, even so, it still carries with it the same peculiar disadvantages. The raising of fees offers an effective escape from

so frequently disrupt office hours. Confidence in the individual physician would be replaced by confidence in the group as a whole.

Even as these lines are written, there are heartening signs that the greater resources and gathering strength of the nations opposed to the Axis Powers are gradually turning the tide. There is a prevailing confidence that the war will not only be won but the peace also, and that we will live in a better world. There will be many changes in our order of living, some of which will certainly concern the practice of medicine. We should proceed on the concept of the greatest good to the greatest number, stress the importance of medical counsel in attaining this end through any legislative means, and finally strive for a better adjustment between the work to be done and the life to be lived as visioned in Utopian Obstetrics.

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### DETAILED TECHNIQUE OF A MODIFIED LOCAL ANESTHESIA FOR CESAREAN SECTION\*

ALFRED C. BECK, M.D., BROOKLYN, N. Y.

(From the Long Island College Hospital)

FOR the past twenty years we have been doing cesarean sections under local anesthesia at the Long Island College Hospital. At first very few were successful. Oftentimes they were more vocal than local, in that the patient complained vociferously, or an incessant chattering by an attendant was necessary to distract her attention. Because of its many advantages, however, we persisted until we now have a satisfactory technique, which is used routinely for all cesarean sections.

Under procaine anesthesia temperature and pain sensation are lost before the sensations of touch and pressure disappear. For this reason the patient often feels the manipulations of the operator without experiencing any pain. In order that her anxiety may not be increased, the tissues are handled as gently as possible and wide retraction is avoided. Adhesions are severed with a knife and not separated by blunt dissection. Unnecessary traction on the uterus, sutures, and clamps is never permitted. Because the manipulations required for the removal of the child and the placenta are too vigorous for many local anesthetics, brief analgesia is induced with nitrous oxide while these manipulations are carried out.

\*Read by invitation, at the Atlanta Meeting of the South Atlantic Association of Obstetricians and Gynecologists, February 6, 1942.

the one whom she would prefer for consultant or assistant. But unless this privilege is restricted to occasions of real importance, the plan loses its benefits to both the patients and the group members.

The benefits to the patient far outweigh the disadvantages. At the office, appointments are kept on time, much to the betterment of the patient's disposition and the satisfaction of those who may have brought her to the office. The patient is impressed by the fact that the doctor seems to have ample time to examine her thoroughly and answer her questions in an unhurried manner. She does not have to experience the inconvenience of leaving the office without being seen, due to a hospital or outside emergency which suddenly interrupts office hours. Furthermore, she feels her office visit is more worth while if the doctor is alert and wide-awake, than if he is nodding or momentarily dozing in her presence.

At the hospital, each shift during labor brings to the patient the advantage of consultation, as agreement is reached on what procedure or treatment will best serve the mother's and baby's welfare. By analogy this practice has been an accepted procedure in the nursing care of patients for many years. Indeed, the patient would be one of the first to object if twenty-four-hour duty was imposed on her nurse.

From the doctor's standpoint what objections may be raised to this manner of obstetric practice? Objections will arise unless the members composing the group are congenial, conscientious, honest, and able to instill confidence in patients. Each member should be well grounded in the basic fundamental principles of obstetrics and able to standardize on the details as well as the essentials of prenatal care. Harmony of this degree could perhaps be attained more successfully if the members of the group received their training from the same clinic or under the same Chief.

Some would consider the division of income as the greatest difficulty to surmount. It is not my intention to present in detail a financial set-up that would meet with universal approval. Suffice it to say that one cannot have his cake and eat it too.

The rewards of longer, more enjoyable and abundant life, opportunities for recreation, rest, travel, study, research, visiting, and learning from one's contemporaries, and last, but not least, the knowledge that patients can be treated more satisfactorily, far outweigh the question of whether one might do better financially by practicing alone. On these premises, it should not be difficult for a group to divide, on a percentage basis and with due regard to seniority, what remains after routine office expenses have been paid.

Such a plan of practice would seem applicable not only to obstetrics, but to pediatrics, surgery, and other specialties. It would seem highly desirable in general practice in which obstetric cases and emergencies

450 mg. per kg. of body weight.<sup>1</sup> If human susceptibility is similar to that of these laboratory animals, at least 25 Gm. would be required to kill a woman weighing 130 pounds. When the drug is injected into a vein, however, only 50 mg. per kg. are required to cause death in the same animals. Its toxicity accordingly is increased almost tenfold whenever procaine is introduced directly into the circulation. The greatest dangers which accompany the use of this drug therefore are its accidental injection into a vein and its rapid absorption in very vascular tissues. Because the tissues injected in our technique are relatively avascular, the latter danger is very slight unless the needle is unintentionally passed into the substance of the rectus muscle in the vicinity of the deep epigastric vessels. The risk of introducing the solution directly into a vein also is slight if the needle is kept moving throughout the injection. As an added precaution, the plunger should be withdrawn slightly before the major portion of the injection is forced into the tissues in order that the entrance of the needle into a vein may be revealed by the presence of blood in the syringe.

TABLE I. DURATION OF PROCAINE ANESTHESIA (HIRSHFELDER AND BIETER)

| EPINEPHRIN CONTENT | MINUTES OF ANESTHESIA |
|--------------------|-----------------------|
| 0                  | 16.6                  |
| 1-500,000          | 83.0                  |
| 1-100,000          | 87.2                  |
| 1,200,000          | 89.2                  |
| 1-500,000          | 65.4.                 |

While the supposed lethal dose may be as large as 25 Gm. for the average person, less than one-tenth of this amount of procaine may cause toxic manifestations. These include nervousness, anxiety, talkativeness, tremor, nausea, vomiting, and a fall in blood pressure. As most of these symptoms also follow the use of adrenalin, some of the unsuccessful results of local anesthesia which are attributed to an unsatisfactory choice of patients or to the employment of a faulty technique, probably are due to the use of too much of one or both of these drugs. According to the majority of writers not more than 1 to 1½ Gm. of procaine and 15 min. of adrenalin should be used. We formerly exceeded these amounts in some cases and the toxic manifestations mentioned militated against a good result. At present we are able to obtain satisfactory anesthesia within the recommended limits.

#### TECHNIQUE

All injections are made with a 10 c.c. syringe to which lateral and plunger rings are attached to facilitate backward and forward movement of the plunger. This type of syringe is preferable to the various constant flow devices since the latter offer no means of determining whether a vein has been entered. Twenty-five gauge three-fourths-inch needles are used for the skin and 22 gauge 3-inch ones for the deep injections.

Unfortunately the drugs which usually are relied upon to relieve the patient's anxiety when local anesthesia is employed, cannot be given preliminary to a cesarean section because of their effect on the child. After the operation is started and shortly before the child is removed from the uterus, one-third of a grain of pantopon and  $\frac{1}{200}$ th of a grain of scopolamine are given for this purpose. Because vomiting occasionally follows the use of morphine, pantopon is preferred.

To obtain the maximum effect with a minimum of drugs three different solutions are used.

Solution 1 consists of 50 c.c. of  $\frac{1}{2}$  per cent procaine without adrenalin. It is employed for the intradermal and subcutaneous infiltrations which anesthetize the site of the incision. Because slight sloughing sometimes occurs when adrenalin is used in these intradermal injections and because prolonged anesthesia in this region is secured by the subsequent deeper nerve blockings, adrenalin is omitted from this first solution.

Solution 2 is prepared by adding 1 c.c. of 1-1000 adrenalin to 200 c.c. of 1 per cent procaine. This 1 per cent procaine and 1-200,000 adrenalin solution is used only for the deep nerve-blocking injections which are made in the vicinity of the semilunar lines at the outer border of the recti muscles. By blocking the nerves before they give off their terminal branches, these injections anesthetize the entire thickness of the abdominal wall from the skin to the peritoneum inclusive. In its action on nerve fibers, procaine affects the smaller relatively thinly medulated fibers more readily than it does the larger more thickly medulated nerves. For this reason a  $\frac{1}{2}$  per cent solution is less efficacious in blocking the larger nerve elements which are adjacent to the lineae semilunares.<sup>1</sup>

Solution 3 is made up of 50 c.c. of  $\frac{1}{2}$  per cent procaine to which  $\frac{1}{4}$  c.c. of 1-1000 adrenalin is added. It is used to infiltrate the peritoneum on each side of the bladder and over the lower part of the uterus. If at any time in the course of the operation additional injections are required, this solution rather than the stronger one is selected. Should the anesthesia wear off by the time the abdominal incision is to be closed, the peritoneum is infiltrated with Solution 3 before it is sutured. Additional injections into the fascia and skin seldom are necessary.

Although it is well known that the addition of adrenalin prolongs the anesthesia produced by procaine, the effect of various dilutions of this adjuvant is somewhat different than might be expected. Hirshfelder and Bieter have shown that 16.6 minutes of anesthesia produced by procaine alone may be prolonged to eighty-three minutes by adding 1-50,000 adrenalin and that it may be prolonged still further to 89.2 minutes by diluting the adrenalin solution to 1-200,000. From Table I it may be seen that the greatest prolongation of the anesthesia and the least danger of toxic symptoms may be obtained by the use of a 1-200,000 solution.<sup>2</sup>

#### DANGERS

The lethal dose of procaine used in the manner described is unknown for man. In the guinea pig, rabbit, and cat it averages 430, 460, and



muscle. A 22 gauge 3-inch needle is then introduced into the incised tissues as near as possible to the fascia and passed outward to the outer border of the right rectus muscle. After testing to determine whether a vein has been entered, 2 c.c. of 1 per cent procaine in 1-200,000 adrenalin (Solution 2) are forced into the region adjacent to the linea semilunaris (Fig. 2). Similar injections are made at intervals of 1 cm. on each side of the wound as shown in Fig. 3. At the upper and lower angles, the needle is passed obliquely in order that the injections may

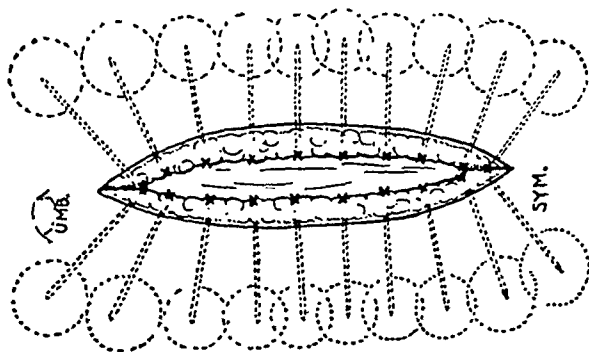


Fig. 3.—Diagrammatic representation of the wheals produced by the deep injections.

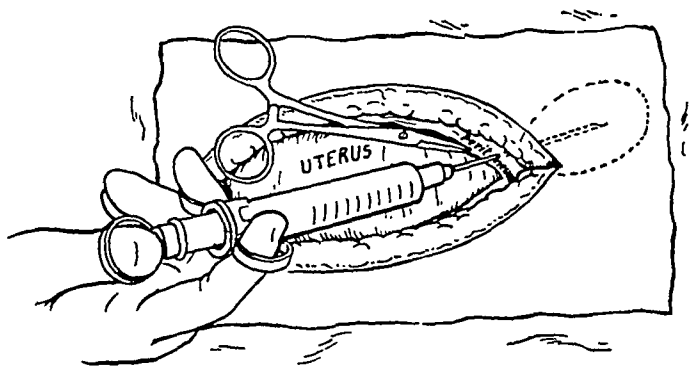


Fig. 4.—After making traction on the peritoneum, 5 c.c. of Solution 3 are injected into the subperitoneal tissues on each side of the bladder.

extend beyond the limits of the incision. A slightly larger amount of the solution also is introduced into these areas. Cross section of the abdominal wall in the region described shows the ease with which fluid placed near the linea semilunaris may diffuse through the fascia and reach the nerves which pass inward between the transversalis and internal oblique muscles to pierce the rectus sheath. If the injections are made correctly, a continuous mass of 1 per cent procaine is placed along this area on each side of the incision in order that it may infiltrate through the fascia and block the nerves before they give off the terminal branches which supply the abdominal wall from the peritoneum to the skin.

At this stage an attendant is requested to note the time and tell the operator when ten minutes have passed. As this interval is necessary for the blocking of the nerves, the operator must wait the full ten minutes before continuing the operation. Since the ligation of the superficial vessels is the only thing that can be done in the interval, this wait-

The point of the needle is introduced into the skin slightly to the left of the midline and a small amount of  $\frac{1}{2}$  per cent procaine without adrenalin (Solution 1) is injected intradermally. The needle is then plunged through the skin and 1 c.c. of the solution is forced into the subcutaneous tissues. As anesthesia is almost immediate within the

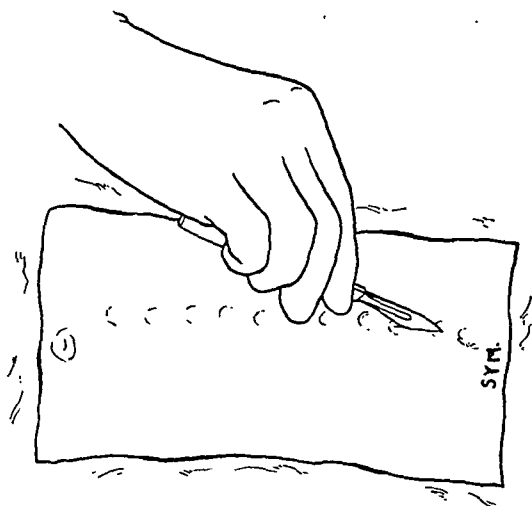


Fig. 1.—Incision of the skin through the line of intradermal wheals.

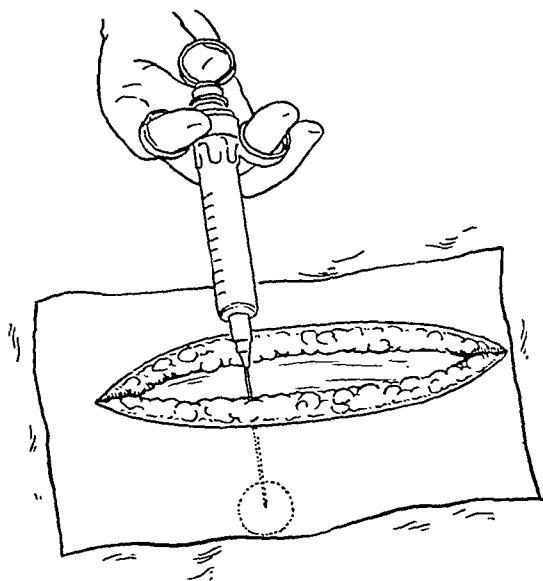


Fig. 2.—Deep injection to block the nerves. The needle is introduced at the junction of the fascia and subcutaneous tissues and the injection is made in the region of the semilunar line.

intradermal wheal, the needle is painlessly reintroduced near its periphery and a second wheal and subcutaneous injection are made. These intradermal and subcutaneous injections are repeated until they extend somewhat beyond the extremities of the purposed line of incision (Fig. 1). About 25 c.c. of Solution 1 are required for this purpose.

Following a brief delay to allow for complete anesthesia, the skin and subcutaneous tissues are incised down to the fascia over the rectus

The inner margin of the rectus muscle is separated from its sheath and the peritoneum is exposed. During this step of the operation, slight traction on the fascia is made with clamps to facilitate the dissection and reveal any possible inadequacy of the anesthesia.

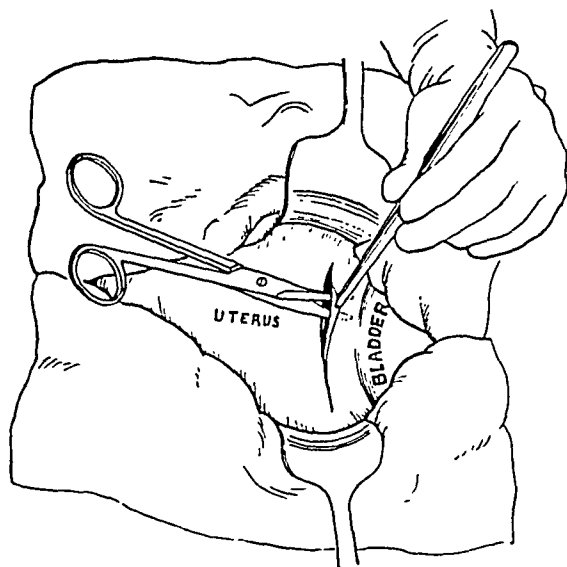


Fig. 7.—After making the transverse incision through the peritoneum, the closed Mayo scissors are introduced on one side of the midline then opened and withdrawn.

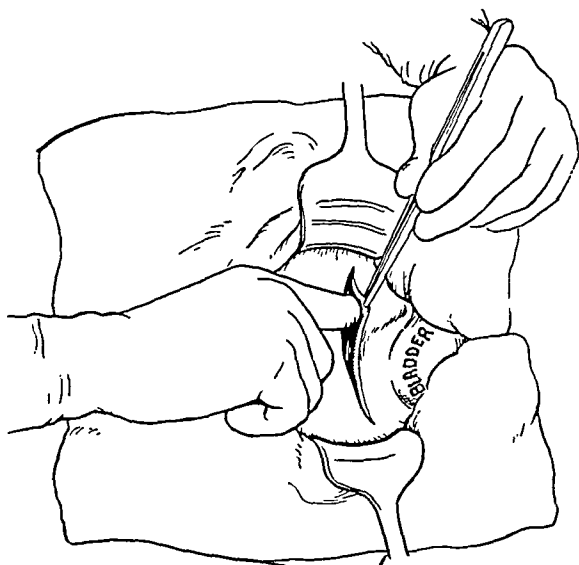


Fig. 8.—The finger is introduced into the area dissected free by the scissors and by a side-to-side movement completes the dissection. By the same technique the bladder and its reflection are dissected through on the opposite side.

The peritoneum is then grasped with clamps and incised. If the nerve block is satisfactory, as it usually is, this can be done without further use of procaine. If it is not, the clamps will cause discomfort and the peritoneum should be injected with  $\frac{1}{2}$  per cent procaine and 1-200,000 adrenalin (Solution 3) before the incision is made.

ing period is the most difficult part of the procedure. The success or failure of the local anesthesia, however, depends upon its strict observance.

After the required time has elapsed, a small incision in the fascia is made with a knife and this is enlarged with scissors. Scissors are used because they may cause slight discomfort in imperfectly anesthetized tissues which otherwise might be incised painlessly with a knife. Should

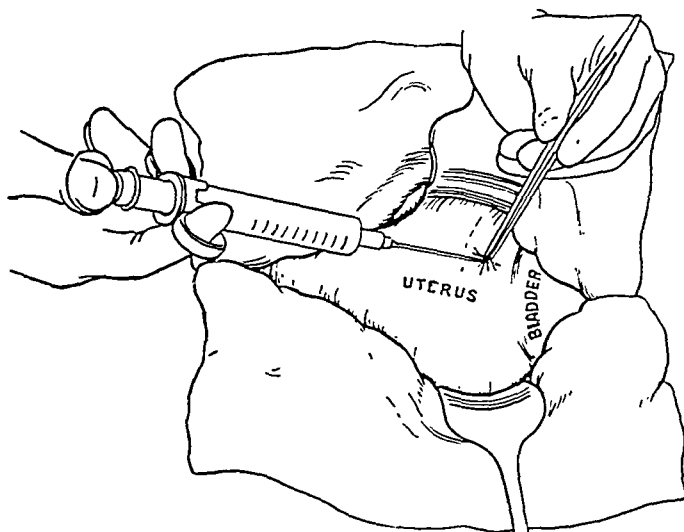


Fig. 5.—After picking up the peritoneum with smooth pointed forceps, 10 c.c. of Solution 3 are injected beneath the bladder reflection.

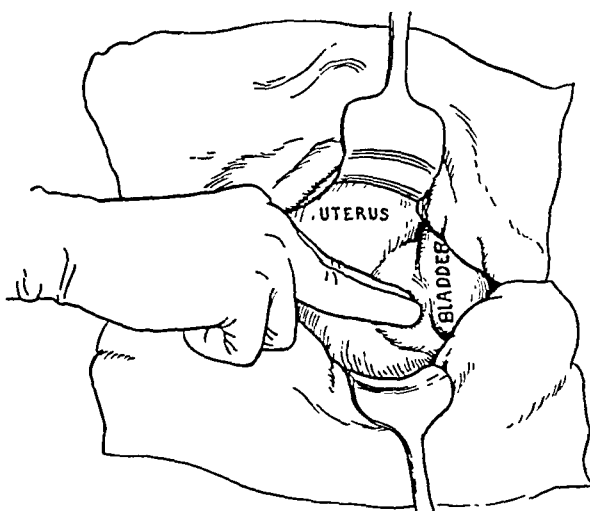


Fig. 6.—Pressure over the wheal causes the dissemination of the solution beneath the bladder and its reflection.

their use show the anesthesia to be imperfect, a slightly longer interval of waiting is indicated. Following this, further procaine is required if the sensitiveness is not eliminated. On the other hand, an absence of discomfort when the scissors are used is indicative of perfect anesthesia, and the operator may proceed with the assurance that even the peritoneum may be incised without pain.

the space thus formed the finger is introduced and by a side-to-side motion dissects off the peritoneum and bladder from the lower segment and cervix (Fig. 8). After repeating this step on the opposite side, the adhesion in the midline is cut and the bladder is pushed off from the uterus.

If advisable, an upper flap is prepared similarly by blunt dissection.

Before the uterus is incised one-third of a grain of pantopon and 1-200th of scopolamine are given and the administration of nitrous oxide is started. During this time the uterus is incised with a knife and the incision is enlarged with scissors. The child is removed head first manually and the nitrous oxide is then discontinued (Fig. 9). Nitrous oxide is given for a very short interval only, not much over one minute, and produces analgesia without anesthesia since the patient usually hears the first cry of the child. If the nitrous oxide is given

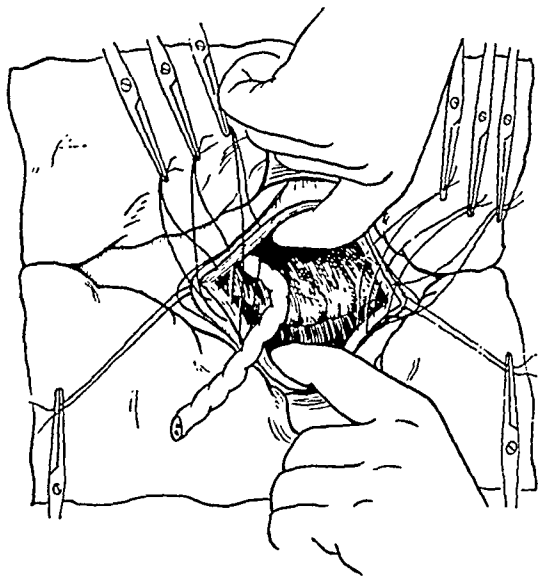


Fig. 11.—After introducing all of the deep sutures, the uterine wound is spread apart and the placenta is removed manually. Following the removal of the placenta, the uterine wound is temporarily closed by making traction on the clamps which hold the deep sutures and the sutures are then tied individually. While the placenta is being removed, nitrous oxide 85 per cent is again given for about one minute.

over too long a period, the patient may become restless and force the intestines into the field of operation. Immediately after the delivery of the child, 1 c.c. of ergotrate is injected hypodermically and interrupted sutures are introduced through the muscle down to the endometrium (Fig. 10). These sutures are placed  $1\frac{1}{2}$  cm. apart and are left long. After they have been introduced throughout the length of the wound, nitrous oxide is again administered for about one minute. The wound is then spread apart so that the hand may be introduced for the removal of the placenta (Fig. 11). The placenta is separated and removed manually. Immediately after the removal of the placenta, the nitrous oxide is discontinued. Here again it is important that the administration of the gas be as brief as possible in order that the patient may not get out of control.

The uterus is closed by making traction on and tying the previously introduced sutures. By waiting a few minutes before removing the

After incising the peritoneum, traction is made on one side at the junction of its middle and lower third and 5 c.c. of Solution 3 are injected into the subperitoneal tissues on that side of the bladder (Fig. 4). This is followed by a similar infiltration on the opposite side.

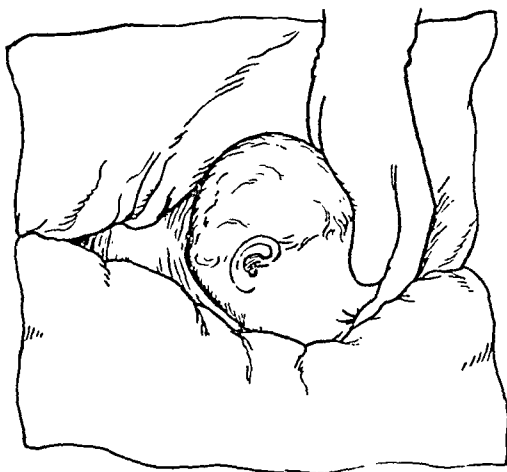


Fig. 9.—After the flaps have been prepared and before incising the uterus one-third of a grain of pantopon and 1/200th of scopolamine are given. The uterus is incised in the midline with a knife and the incision thus made is enlarged with scissors. During this procedure nitrous oxide (85 per cent) is given for one minute. The hand is introduced into the uterus and acting like a vectus assists in the delivery of the child's head. Forceps are very seldom used. During the delivery of the child nitrous oxide is continued but is not given for much more than one minute.

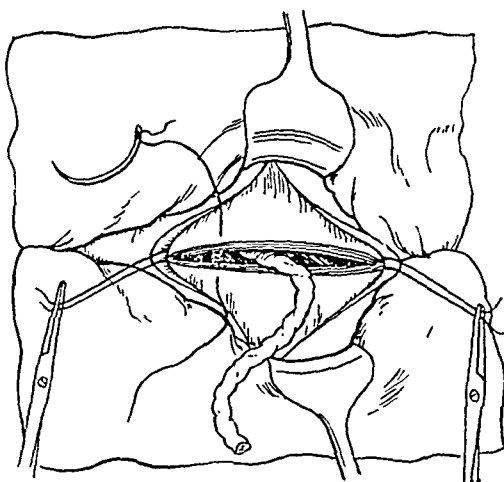


Fig. 10.—Deep interrupted sutures are introduced through the entire thickness of the uterine muscle down to the endometrium. While these interrupted sutures are being introduced, the placenta is not disturbed.

Smooth-pointed forceps now pick up the peritoneum on the anterior surface of the uterus about 1 inch above the bladder, and 10 c.c. of 1/2 per cent procaine and 1-200,000 adrenalin (Solution 3) are injected beneath the bladder reflection (Fig. 5). Pressure on the wheal thus made, disperses the fluid toward the sides and under the bladder (Fig. 6).

The peritoneal reflection is incised transversely and scissors are passed beneath on one side, opened, and withdrawn (Fig. 7). Into

Because of its safety many men select this type of anesthesia in cases of toxemia, respiratory infection, diabetes, heart and kidney disease. If it is best in these serious cases, it certainly should be best for the ordinary cases as well.

Under local anesthesia the contraction and retraction of the uterus is not interfered with as it is when general anesthesia is used. The tendency toward hemorrhage from the placental site during and immediately after operation is greatly diminished. This is an important advantage when the operation is done before the onset of labor or in the presence of uterine atony late in labor. The freedom from circulatory disturbance together with this lessened tendency toward hemorrhage greatly reduces the possibility of the occurrence of shock.

The general condition of the patient immediately after operation is so good and her convalescence is so much better than after general anesthesia that even the operators who have trouble in obtaining satisfactory anesthesia by means of the local technique are reluctant to discontinue its use.

Fluids can be taken by mouth before, during, and immediately after operation. Thirst accordingly either does not occur or is easily relieved. Sweating also is seldom observed and the dehydration which is so common after most major operations is greatly reduced or entirely eliminated.

Vomiting during and after operation does not occur unless excessive amounts of the drugs are given. As a result the stomach need not be empty at the time of operation. For the same reason aspiration pneumonia and plugging of the bronchia do not occur. Because the decision to operate often is made after labor has started and after food has been taken this freedom from gastric disturbance and its sequelae is one of the chief reasons for the selection of local anesthesia.

Foods are ingested within a few hours after the patient returns to her room. Because of this and because the intestines are seldom seen during the operation, distention and gas pains are much less frequent than after general anesthesia.

The heat regulating mechanism is not disturbed and abnormal sweating and chilling of the body surface do not occur.

Since the respiratory tract is not irritated as it is when inhalation anesthesia is used, the bronchial secretion is not increased and latent infection in the lungs is not activated. For this reason and because the absence of vomiting eliminates the possibility of aspirating gastric contents, pneumonia and massive collapse of the lungs seldom occur. The lack of respiratory irritation also makes possible the use of cesarean section in women who ordinarily would be considered poor risks because of the presence of an upper respiratory infection.

The gentle handling of the tissues required by the local technique coupled with the fact that the patient is active almost immediately after

placenta, the uterus becomes retracted and is better able to control bleeding from the placental site than it is when the placenta is removed immediately. Additional sutures are introduced wherever necessary. The upper flap is brought down over the upper angle of the uterine wound and following this the lower flap is brought up over the upper one and sutured (Fig. 12).

Some patients go to sleep soon after the placenta is removed. Most of the others are quiet and free from anxiety.

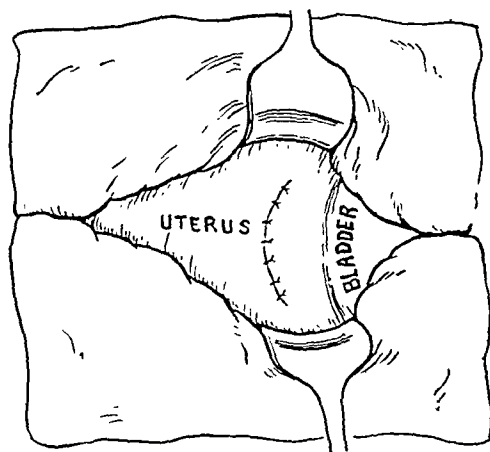


Fig. 12.—The uterine wound is closed and covered with peritoneum. If the parietal peritoneum is sensitive when it is sutured, a small amount of Solution 3 should be injected into the subperitoneal tissues adjacent to it.

The abdominal wound is closed in layers. This usually can be done without further anesthesia. If the anesthetic has worn off, however, the peritoneum is infiltrated with Solution 3 before it is sutured. It is not necessary to reanesthetize the fascia and skin.

The amounts of the various solutions generally required for the entire operation are shown in Table II. By using different dilutions, the quantities of procaine and adrenalin are considerably reduced. Only 1 to 1.3 Gm. of procaine and 9 to 11 min. of adrenalin are required in most cases. At the same time ample solution (120 to 160 c.c.) is available for all steps of the procedure.

TABLE II. AMOUNTS OF PROCAINE AND ADRENALIN USED

|            | C.C.    | PROCAINE CONTENT<br>GM. | ADRENALIN CONTENT<br>MIN. |
|------------|---------|-------------------------|---------------------------|
| Solution 1 | 20-30   | 0.15                    | 0                         |
| Solution 2 | 80-100  | 0.8-1                   | 6-8                       |
| Solution 3 | 20-30   | 0.15                    | 3                         |
| Total      | 120-160 | 1.1-1.3                 | 9-11                      |

#### ADVANTAGES

The chief advantage of local anesthesia lies in the fact that its use is accompanied by little or no immediate risk of death. I do not know of nor have I heard of a single instance in which death occurring during or immediately after a cesarean section was attributed to local anesthesia. I am unable to say the same for any other anesthetic agent.



Since then there has been some dissent from these findings. Kanter, Klawans, and Bauer,<sup>6</sup> in a careful study of 100 patients with fibromyomas, found hyperestrinism to play a part, but not the only one in the etiology, and they conclude that various factors must be associated. They found endometrial hyperplasia in 55 per cent of 100 cases. Light<sup>7</sup> in 100 cases showed hyperplasia in only 17 per cent and Reis<sup>8</sup> in 18 per cent. Bowers,<sup>9</sup> in a study of 476 cases, reported endometrial hyperplasia in 11 per cent. Brewer and Jones<sup>10</sup> found it in only 1 per cent of 100 carefully studied cases. Henderson<sup>11</sup> found swiss-cheese type hyperplasia of the endometrium in 6.5 per cent of the uteri of 727 fibromyomatous patients.

These varying percentages of coincident hyperplasia may be due to different criteria of what is hyperplasia, an entity only recently widely introduced to pathologic study. Furthermore, the interpretation of the pathology of the endometrium may vary with the cyclic stage of removal.

In attempts to show the influence of estrogen on the production of fibromyomas, Nelson<sup>12</sup> injected 32 guinea pigs with various estrogenic substances over periods of two to ten months and was able in 6 cases to produce fibromyomatous growths in and about the uterus. These were associated with adenomatous hyperplasia of the endometrium with hemorrhage and metaplastic surface epithelial changes in the cervix with hyperkeratinization. The hyperplasia of the endometrium was made to disappear by injections of one-fifth to one-half rabbit units of progestin daily for ten days. Since the pioneering work of Nelson, a dozen or more papers have been published by Lipschutz, Vargos and associates in Chile.<sup>13-20</sup> Their thoroughly documented and well-illustrated studies may be summarized as follows: Using large doses of various esters of estradiol, injections or pellets, they produced in castrated female guinea pigs fibrous growths, usually subperitoneally about the uterus or other organs in the abdominal cavity. If they used small doses they produced hyperplasia of the endometrium and metaplasia of the cervical mucosa. Neither of these conditions developed if the injections were intermittent. In order that the condition develop, the doses had to be given continuously. Prevention of the development of the new growths of hyperplasia was achieved also by simultaneous introduction of progesterone and testosterone. The growths were fibrous tissue only, not fibromyomatous, and usually were not in the myometrium. They occurred in the abdominal cavity, but never in the thoracic cavity.

Our study embraces 1,741 fibromyomas and the associated pathology found at operation in this community during the past twenty years. The 1920 census population was 60,211; the 1930 census, 60,342; the 1940 census, 65,919. The Department of Commerce reports 58 per cent white and 42 per cent Negro. The white population is essentially colonial English descent. Approximately 5 per cent of whites and 5 per cent of Negroes came here for operations from out of the city.

The pathologic study includes practically all of the operations done in the region during twenty years. Several pathologists have taken part in recording the observations, but the findings were carefully and fully

the operation diminish the risk of thrombosis and embolism, postoperative complications which are not infrequent after ordinary cesarean section.

When this technique is followed, the child is not affected by either the analgesic drugs or the anesthetic agents. As a result, the child cries spontaneously as soon as it is taken from the uterus. Anoxia and respiratory difficulties, accordingly, are absent in all cases in which the child's condition is satisfactory at the beginning of the operation.

#### DISADVANTAGES

The only disadvantages are that it is time consuming, requires gentle handling of the tissues, and tries the patience of the operator. With practice it can easily be mastered and the satisfaction of achievement will then reward the surgeon for his perseverance.

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20 LIVINGSTON STREET

## THE ETIOLOGIC AND PATHOLOGIC FACTORS IN A SERIES OF 1,741 FIBROMYOMAS OF THE UTERUS\*

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THE literature of fibromyomas of the uterus in the past ten years stresses etiology especially in regard to the reproductive hormones. One of the first to write upon this subject was Moench,<sup>1</sup> who in 1929 suggested the female sex hormonal influence upon the development of the tumors, based upon the observations that the tumors develop only during the active sex and reproductive life of the woman.

This theory was greatly amplified and given widespread appreciation by Witherspoon<sup>2-4</sup> in 1933 to 1935, who ably argued that the causative factor must be the estrogenic hormone. The main basic fact was the association of hyperplasia of the endometrium with fibromyomas, which he found to be as high as 55 per cent. This theory was supported by King.<sup>5</sup> These two also thought that chronic pelvic infection played a part in excess production of estrogens by ovarian congestion.

\*Read at the Fifth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Atlanta, Ga., February 6 and 7, 1942.

*Pelvic Infection.*—In the 575 cases in white women, salpingitis occurred 93 times (16.2 per cent), while in the Negroes it was present in 633 cases (54 per cent) of the 1,166. Forty per cent of all patients operated upon for chronic salpingitis here had fibromyomas.

Moench and Witherspoon are of the opinion that the presence of infection and hyperemia have much to do with increased ovarian activity of estrogenic type, with tendency to suppression of the corpus luteum. However, in this study corpus luteal cysts were by no means absent. In the 575 white women there were found at least 67 follicular cysts and 43 luteal cysts. In the 1,166 Negro cases, there were at least 225 follicular cysts and 117 luteal cysts. Possibly more pathology of similar type may have been present in ovaries which were not removed. Brewer and Jones<sup>10</sup> found ovarian changes to approximate those found in normal pelvises. Adenomyosis began to be recorded only after 1926, but since then appeared quite uniformly year after year, there being 21 cases among the 575 white patients (3.6 per cent) and 18 among the 1,166 Negroes (1.5 per cent).

*Degeneration.*—Necrosis was found in 45 fibromyomas of the 575 white women (7.8 per cent) and in 190 tumors of the 1,166 Negro women 16.2 per cent. One would naturally suspect that the incidence of necrosis would be greater in the earlier reports when operations were deferred longer than in recent years. However, that does not appear to be the case in this series. Necrobiosis is the result of vascular changes usually on the venous side, so that congestion, hyperemia, edema, diapedesis and thrombosis are more common than anemic infarction. Pregnancy has long been known to be associated with red degeneration which is essentially incomplete interference with venous circulation, and no doubt pelvic infection has a similar effect. Rapidity of growth certainly ought to be accompanied by greater incidence of vascular degeneration. Consequently, the more frequent occurrence of necrotic changes in the tumors of Negro women is evident. Likewise, calcification, which is an end stage of necrosis, is more frequent in the Negro, occurring 50 times in the 1,166 cases and 14 times in the 575 white cases.

Pure myomas were found in 11 white patients and in 37 Negro patients. Adenomyosis of the uterine wall or of the fibromyoma occurred in 21 white women (3.6 per cent) and in 18 Negroes (1.5 per cent).

A record of the ovarian cysts revealed, in addition to the incidence of follicular and corpus luteum cysts, 11 cystadenomas in the white patients. Three of these were malignant. In the Negro patients there were 12 such cysts and 5 were malignant. Dermoid cysts of the ovaries occurred in nearly 1 per cent of the white patients (5 cases) and in  $2\frac{1}{3}$  per cent of the Negroes (26 cases).

The following were rare complications: tubal pregnancy, 2; large cystic degeneration of the tumors, 2; ovarian fibromas, 2; solid ovarian carcinomas, 1; ovarian hemangiomas, 2; bilateral Krukenberg tumors, 1; mesotheliomas, 1; adenocarcinoma of the appendix, 1; adenocarcinoma of the sigmoid colon, 1.

Record of the state of the endometrium in each case in this study was not made because it has only been recently that accurate criteria in regard to hyperplasia have been accepted. However, in the past four years the endometriums from all uterine specimens have been studied and recorded according to the definitions of hyperplasia of Cullen,<sup>26</sup> and Novak and Martzloff.<sup>25</sup>

described and often illustrated by hand drawings. With the exception of adenomyosis, the incidence of the entities is quite uniform from year to year.

*Race Incidence.*—Of the 1,741 cases, 575 occurred in white women and 1,166 in Negroes. Since, in the ratio of white to Negro, the population here has been quite uniformly 58 to 42, the corrected ratio of incidence in the white to that in the Negro is as 479 to 1,457 or 1 to 3.3. The principal value of this study lies in those figures, for we know of no other where the essential factors are under such control. Most studies are made in large cities where the population is fluctuating, where certain economic strata of the population are concentrated at various hospitals, so that an accurate incidence cannot be ascertained. Miller,<sup>21</sup> in New Orleans, in 1924, concluded that fibromyomas were nine times as frequent in Negroes as in white women. He analyzed only 150 cases, and Lewis in the discussion dissented from this high incidence. Alsbrook,<sup>22</sup> in New Orleans, in 1931, in a study of 1,000 cases, estimated that the condition was five times more frequent in the Negro than in the white race. Cohen,<sup>23</sup> also of New Orleans, in 1930, analyzed 1,000 cases, 897 in Negro women and 103 in white. Levy,<sup>24</sup> in New Orleans, in a study of 5,821 patients operated upon for fibromyomas, found 12.2 per cent in white and 87.8 per cent in Negro women.

The greater incidence of the fibromyomas in the Negro women and their apparently more rapid growth may be associated with the greater tendency of keloid development in the Negro. (For the past five years here all of the post-operative keloid scars in gynecology patients have been recorded along with the reason for operation. It will be interesting to ascertain the coincidence of fibromyomas in those patients.) Along this same line there is a great tendency for development of large fibrous tumors in the Negro afflicted with lymphogranuloma. While it is true that white individuals have this infection, they seldom develop such tumors.

*Age.*—The youngest white woman was 18 years and the oldest white woman, 76 years. The youngest Negro woman was 17 years and the oldest Negro, 75 years. The greatest age incidence in the white patient ranged from 37 to 46 years inclusive and in the Negro patients from 29 to 42 years inclusive. The average age of the white woman in this series was 39 or 40 years, while that of the Negro woman was 36 or 37. This race relationship is identical to that found in a similar study of the incidence of eclampsia.

*Size of the Tumors.*—In the vast majority of cases the tumors were multiple. In most cases a record was made of the diameter of the tumors in centimeters. Five centimeters was the dividing line arbitrarily chosen to illustrate the size, large or small. Thus 301 white women had tumors smaller than the diameter of 5 cm., and 197 had tumors larger than 5 cm.; 302 Negro women had tumors smaller than 5 cm. while 586 had large tumors. In other words, 60 per cent of the white women had smaller than 5 cm. tumors and 40 per cent had large; 34 per cent of the Negro women had small tumors and 66 per cent had large. The Negroes had, then, not only three and one-third times the incidence, but they had  $1\frac{1}{2}$  times the incidence of the larger tumors.

6. Complicating ovarian changes revealed follicular and corpus luteum cysts to be relatively frequent, cystadenoma to be present in 2 per cent of all fibromyomas, and dermoid cysts in 1 per cent of the white and in 2 per cent of the Negro patients.

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A comparison has been made in regard to the endometrial findings in 100 fibromyomatous uteri and in 100 nonfibromyomatous uteri of recent date.

In these 200 cases 20 per cent of the white fibromyomatous uteri and 10 per cent of the Negro fibromyomatous uteri had hyperplasia of the endometrium. Of the nonfibromyomatous uteri removed for chronic salpingitis or for bleeding late in the reproductive life associated with chronic cervicitis, etc., about 15 per cent of the white patients and 20 per cent of the Negro patients had hyperplasia. This quite definitely indicates that there is no special association of endometrial hyperplasia with fibromyomas. This is in agreement with the findings of Brewer and Jones<sup>10</sup> in a study of 100 patients with fibromyomas, in which they found that ovulation, corpus luteum development, and endometrial response were identical to that found in women without fibromyomas. If this then is true, it deletes one of the important arguments in favor of hyperestrinism as the sole etiologic factor in fibromyomas. The studies of Witherspoon, Nelson, Lipschutz and Vargos, and others, quite distinctly indict the female sex hormone as the etiologic factor, but are not convincing as to the exact mechanism. It may be that there is a lowered threshold to stimulation to growth in the isolated affected tissues brought on by trauma of menstruation, pregnancy and labor, or of infection.

We hazard the opinion also that the factor may be an altered hormone, probably estrogenic, the aberration being produced by the influence of other hormones as progesterone, or pituitary hormones or by the endometrium or the myometrium. We suggest experiments in which the experimental animals with normal and with traumatized uteri are injected with serum and urine fractions from fibromyomatous patients to attempt production of true intrauterine fibromyomas rather than intra-abdominal fibrous tumors as are produced by estrogenic hormones.

#### SUMMARY

1. The incidence of fibromyomas in Negro women residing in the neighborhood of Augusta, Georgia, is three and one-third times that of white women.

2. Sixty per cent of white women had tumors smaller than 5 cm. in diameter. Sixty-six per cent of the Negro women had tumors larger than 5 cm. in diameter.

3. Chronic salpingitis was found in one-sixth of the white and more than one-half of the Negro patients with fibromyoma. On the other hand, 40 per cent of all operations for chronic salpingitis revealed complicating fibromyomas.

4. Necrosis in general was about twice as frequent in the tumors of the Negro women as in those of the white women.

5. Fibromyomas were found to be relatively free from malignant complications, but sarcomas were more frequent in the Negro, while carcinomas were more common in the white women.

men became smaller and fetal movements could not be felt. Her general health became improved, but an abdominal tumor remained. Bimanual examination gave the impression usually seen in fibroid tumors of the uterus or abdominal pregnancy with retained fetus. The abdomen was opened and a dead fetus of about eight months was in the abdominal cavity. Its sac was attached to the upper portion of the uterus. The placenta was attached to the right broad ligament. The patient made a good recovery.

The fifth case was reported by E. Allen.<sup>5</sup> The patient was a twenty-one-year-old Negro primigravida. The abdominal pregnancy was diagnosed and, while the patient was awaiting term, she had three convulsions. The baby, delivered by laparotomy, weighed four and one-fourth pounds. It cried lustily but died in eight hours. The mother had a psychosis, discharged some placental tissue through the upper end of the wound, but eventually recovered.

The sixth case was reported by Ewart.<sup>6</sup> The patient, 41 years of age, was in the eighth month of her sixth pregnancy. Her fifth pregnancy sixteen years previously was complicated by edema. She had three convulsions. The presentation was a breech and an external version was attempted. Four days later induction of labor was attempted with bougies but was unsuccessful. A month later laparotomy revealed the true condition, i.e., abdominal pregnancy. The patient died on the third postoperative day. Autopsy showed an internal hemorrhage from the placental side.

Our case is, so far as we can find, the seventh extrauterine pregnancy to be complicated by eclampsia. Furthermore, it is the only ovarian pregnancy that has been reported with such a complication.

Mrs. D. A. W., aged 30 years, pregnant for the first time, was due on May 12, 1940. The patient was an only child. Her family history was negative. The patient had scarlet fever at thirteen years. Except for an occasional attack of "flu" there had been no other illness. She was married in 1936. Menses began at eleven, occurred every 26 to 28 days, and lasted five days. She had leg ache sometimes when she menstruated and a leucorrhea of some years' standing. In May, 1939, she flooded two weeks after a regular period, passed clots, and had some cramps. One of us saw her at this time and considered it a functional bleeding. The patient menstruated last on August 5, the flow lasting two days. From September 9 until some time in November the patient had a little bloody vaginal discharge which was never as much as an ordinary menstruation. She was a little nauseated and had canker sores in the mouth. Pelvic examination showed what was thought to be an enlarged retroverted uterus. No lateral masses were palpated and the examination elicited no pain or discomfort. The Friedman test was positive. On December 1, her face and hands began to swell and she had an attack of severe abdominal pain which was relieved by morphine. This was the only attack of severe pain. There was some dysuria before Christmas and, when on her feet, she experienced some lower abdominal discomfort. On January 23 she had three convulsions and was "out," as the patient expressed it, for six days. At this time she was taken to the hospital. Her blood pressure was 210/120 and the urine was loaded with albumin. The treatment consisted of magnesium sulfate by mouth and once by vein, and sodium amytal.

## ECLAMPSIA AND OVARIAN PREGNANCY\*

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A CAREFUL search of the various medical indices failed to reveal a similar case. Only six instances of extrauterine pregnancy with eclampsia have been reported and these have all been tubal or abdominal pregnancies. The first case was reported by Spiegelberg.<sup>1</sup> The patient was a 32-year-old para iv at term. She had five convulsions before her admission to the clinic. She was edematous, with scanty, dark-colored urine that boiled solid. Fetal heart rate was 128. The cervix was open and pushed to the left. The internal os was closed. The baby was in the R.O.A. position. The patient had three more convulsions after admission. She was given ergot and an attempt was made to introduce a catheter into the uterus. It met with some obstruction and the examining finger brought back a piece of decidual tissue. The patient died two days later and autopsy showed dark bloody fluid in the peritoneal cavity and a beginning peritonitis. The fetus, a male, weighed 3,000 Gm., was entirely within the Fallopian tube which showed some sign of rupturing in one place. The uterus was 12 cm. long.

The second was reported from Maygrier's Clinic in Paris by H. Lafon.<sup>2</sup> The patient was a 27-year-old para iii who early in her pregnancy (July, 1895) had severe abdominal cramps that confined her to bed. In August she had a hemorrhage while in the hospital. In September she had edema of the lower extremities and again entered the hospital where a diagnosis of pregnancy complicated by tumor was made. On February 10 she bled a little and two days later began to have convulsions (18 in all). On February 13 Maygrier made an internal examination and diagnosed the extrauterine pregnancy with living baby. The fits continued and the woman died undelivered. The diagnosis of extrauterine pregnancy was confirmed by post-mortem colpotomy.

The third case was reported from Denmark by Holst<sup>3</sup> (1896), who was called after a young girl had lost consciousness and was having convulsions. He found the uterus to be the size of a six months' pregnancy. The urine contained a quantity of albumin. He made an unsuccessful attempt to induce labor by injecting hot water. The convulsions stopped and the patient improved. Five months later a fluctuating abscess formed which opened into the vagina. Small fetal bones escaped. The abscess also opened into the intestines. The first opening was enlarged and the head and most of the fetal skeleton were evacuated. The fistulas closed quickly and recovery ensued.

Schumann<sup>4</sup> reports the case of a patient, upon whom E. P. Davis operated. The patient was a primipara aged about 30 years. Her pregnancy had proceeded normally until between the seventh and eighth month, when after albuminuria had been present for over a week the patient had several eclamptic convulsions. She recovered from this seizure and, although she had some abdominal pains, labor did not come on. The abdo-

\*Read at the Fifth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Atlanta, Ga., February 6 and 7, 1942.



test indicated that the placenta had ceased to function and, therefore, there was no question but that the fetus was dead. The fact that the uterus did not empty itself and could not be made to empty itself, was the only indication of an extrauterine pregnancy. The contracted uterine body was not visualized on the soft tissue plate. Tissue which had been removed from within the uterus was reported as placental tissue by the pathologist, but this was not conclusive because no villi were found. The presence of decidual cells, according to TeLinde, is not absolute proof that pregnancy exists. We finally agreed on the therapeutic test of giving the patient estrin for five or six days. If the dead fetus lay within the uterus, the estrin would in all probability activate the uterus, especially as the placenta had been shown to be inactive. If the estrin failed, a laparotomy should be done.

An abdominal operation was performed April 13, 1940. The uterus was found to be slightly enlarged, flattened, and resting on top of a large mass, which measured 15 by  $9\frac{1}{4}$  by  $8\frac{3}{4}$  cm. The mass was symmetrical and semisolid. It occupied the cul-de-sac and extended to the umbilicus. No free blood was present in the abdominal cavity. The left tube and ovary were normal. In one place there was a small, thinned-out, discolored area in the gestation wall. This condition was caused, no doubt, by the accidental rupture of the uterine wall and the gestation sac by the sound on Feb. 12, 1940. The mass, attached to the right side of the uterus by a long pedicle, was easily freed by blunt dissection and brought up into the wound. Had one not known that a pregnancy existed, he would have thought this to be an ovarian tumor or cyst on a long pedicle. The right uteroovarian ligament was identified, and the right tube appeared normal, except at the distal end, where it was adherent to the mass. The right ovary could not be seen. Large blood vessels were present in the pedicle, which extended from the uterus to the mass, and were the only source from which the gestation sac received its blood supply. The vessels were ligated and the sac was removed after division of the pedicle. The recovery was uneventful. The patient was discharged from the hospital on May 3, 1940.

#### MICROSCOPIC STUDIES

We are indebted to Drs. C. C. Fenton and G. S. Dodds of the University of West Virginia for the following description of the specimen: "Four samples from different regions of the sac showed the following microscopic structure: The greater portion of the thickness of the wall from the inner surface was of necrotic tissue with much blood. Here and there a necrotic villus was seen. The outermost layer of the wall (1 mm. and less in thickness) was not necrotic and showed definite ovarian structure. The stroma was of connective tissue, well vascularized, and rich in spindle-shaped cells, a histologic picture strongly suggestive of the ovary. Definitely diagnostic were scattered ovarian follicles in various stages of growth, from those of small size to large ones with structure like the usual Graafian follicles (Figs. 2 and 3). All of the larger follicles were greatly flattened in a position parallel to the surface of the sac, as would be expected when the ovary had undergone great distention. (Fig. 2 shows a portion of a follicle which measured 4,000 by 70 microns.)"

"The larger follicles were undergoing atresia, as shown by degeneration of the granulosa cells and by the presence of polygonal theca lutein cells among the spindle-shaped cells of the theca folliculi (Figs. 2 and 3).

Except for dimness of vision the patient recovered completely from the toxemia. The blood pressure became normal and the albumin disappeared from the urine. Her highest temperature was 101.2° F. on January 25. At that time her pulse was 132. Since then her temperature has been normal. Four attempts were made to induce labor. Each time she had a few cramps when the packing was removed. At the third attempt, Feb. 12, 1940, some material was removed which the pathologist reported to be placental tissue with decidual cells and columnar epithelium. However, no villi were seen. The patient had quite a hemorrhage at this time and a small transfusion was given. At this time some doubt arose as to whether the fetus was within the uterus. A Friedman test was repeated and a soft tissue x-ray was taken in hopes of demonstrating the uterus. The Friedman test was negative and the x-ray showed a small fetal skeleton lying transversely just above the

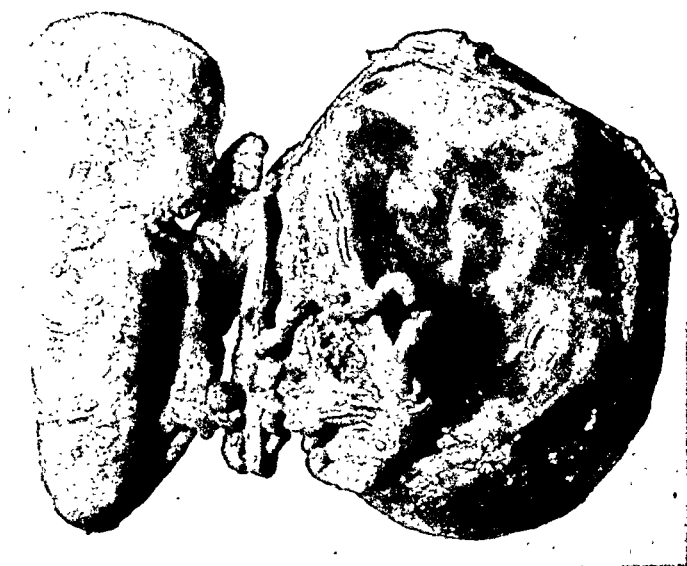


Fig. 1.—Gestation sac opened, showing inside surface of sac and entire fetus.

pubes. No uterine shadow could be seen. The patient was in excellent condition except that she could not read. When she walked about there was a small amount of uterine bleeding. Urine was negative. Blood count was red cells 3,460,000; leucocytes, 13,500; polymorphonuclears, 77 per cent; hemoglobin, 70 per cent; blood pressure, 120/86. Heart and breath sounds were normal. The abdomen was rounded and there was a mass that reached halfway to the umbilicus. Vaginal examination showed marked pigmentation of the mucosa. There was no vaginal discharge. The introitus was nulliparous. The cervix was just back of the pubis. It was soft, uneffaced, and admitted a finger for about an inch. The pelvis was filled with a firm unmovable mass. Examination caused the patient no pain. The abdominal mass could not be outlined by bimanual examination, but seemed to extend about halfway to the umbilicus.

The discussion of the case centered about the question as to whether the fetus was within or without the uterus. The negative Friedman

would seem that nature is performing an experiment for us to see if the location of the placenta made any difference. In Spiegelberg's case the placenta was within the tube. In our case it was within the ovary. In Allen, Schumann, and Ewart's it was in the abdominal cavity and presumably that was true also in Holst's and Lafon-Maygrier's cases. Eclampsia is possible, regardless of where the placenta is located. The next question is the relative frequency of eclampsia when the placenta is implanted in or on tissues outside the uterus. The frequency of eclampsia is variously stated as once in 300 to 500 cases. If the same frequency obtained for ectopic pregnancy, it would mean that there have been from 2,100 to 3,500 cases of misplaced gestation of at least five months' duration. Certainly that many have not been reported.

Clinically this group of 7 extrauterine pregnancies with eclampsia is interesting. Most of the patients complained of the usual symptoms of ectopic gestation, i.e., abdominal pains and vaginal bleeding. The toxemia appeared rather earlier than is usual in uterine pregnancy, only one of the patients being at term. The diagnosis of the ectopic pregnancy was made only once before the convulsions occurred. In this case the baby lived for several hours after it was delivered by laparotomy. In 5 cases the babies died before a correct diagnosis was arrived at. In the second case the correct diagnosis was made while the baby was alive, but the mother died undelivered. In the third case the fetal bones were discharged through a fistulous opening. In the fourth, fifth, sixth, and seventh cases, the fetuses were removed by laparotomy and the induction of labor was attempted in the first, third, sixth, and seventh cases. Three mothers died, two undelivered, and the third of internal hemorrhage after operation. Two recovered after stormy convalescences, and two after uncomplicated convalescences. In our case a diagnosis of extrauterine pregnancy was made before operation. That it was a primary ovarian pregnancy was not suspected until the abdomen was opened. Fortunately, she made an uneventful recovery.

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No germinal epithelium was observed at any of the places sampled, but at one place a mesothelial covering was seen.

"Sections from the wall in the placental area showed many chorionic villi. The superficial zone in these sections was somewhat suggestive of ovarian stroma, but not conclusively so. One probable ovarian follicle of moderate size was seen. On the whole the microscopic studies are sufficient to demonstrate that ovarian tissue was present in the outer stratum of the sac at the several places sampled." Thus the case fulfills all the essential criteria for ovarian pregnancy, viz., (1) the gestational sac occupied the position of the ovary; (2) the tube on the affected side

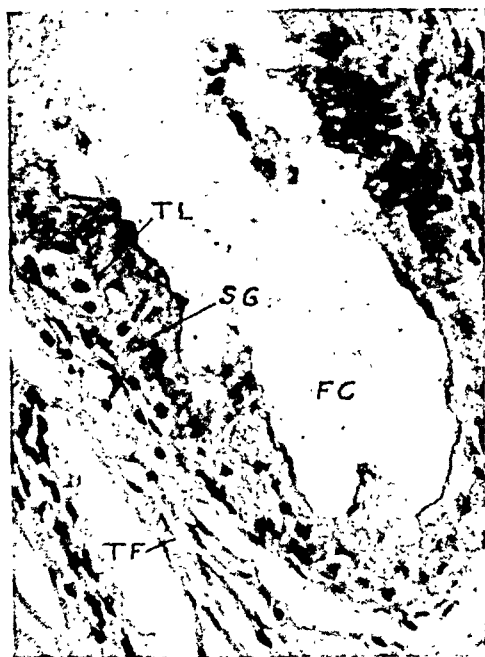


Fig. 2.

Fig. 2.—Part of large ovarian follicle: *FC*, follicular cavity; *SG*, stratum granulosum; *TF*, theca folliculi; *TL*, theca lutein cells. (Photomicrograph under high power.)



Fig. 3.

Fig. 3.—Shows wall of large ovarian follicle and adjacent ovarian stroma including many theca lutein cells and an early follicle (*EF*). (Photomicrograph under high power.)

was intact and showed no evidence of gestation; (3) the gestational sac was connected with the uterus by the uteroovarian ligament; (4) definite ovarian tissue was found in the wall of the sac in different places; and, (5) there was placental tissue within the ovarian stroma.

#### DISCUSSION

The rarity of the combination of eclampsia and ovarian pregnancy is not surprising. In the first place, eclampsia seldom occurs in the first half of pregnancy. Stander<sup>8</sup> says that fewer than 60 cases have been reported. In the second place, ovarian pregnancy is rare and such a pregnancy rarely extends into the second half of pregnancy. The same can be said for extrauterine pregnancy as a group.

We know that the presence of the fetus is not necessary in order to have eclampsia but that the presence of the placenta is necessary. It

balloon of the "Micky Mouse" variety with two ears, which when distended with water fixed themselves in the cornua of the uterus, thereby preventing the expulsion of the balloon. Tracings of uterine contractions were recorded immediately after the third stage of labor and on the fifth, tenth, and fifteenth days of the puerperium. After the normal contractions had been recorded, the patient was given 1 c.c. of obstetric pituitrin subcutaneously and a subsequent tracing was obtained. Two of the patients received a course of estrin therapy after the fifteenth day and the effect of this hormone on the puerperal uterus has been observed.

#### NORMAL PUERPERAL CONTRACTIONS

Examination of the tracings will reveal that the contractions were similar in all 6 cases (Fig. 1). It may therefore be assumed that these tracings represent an accurate picture of uterine motility in the puerperium. Contractions which followed the delivery of the placenta were high in amplitude, recurred on an average of every three minutes, and

PUERPERAL CONTRACTIONS • NORMAL

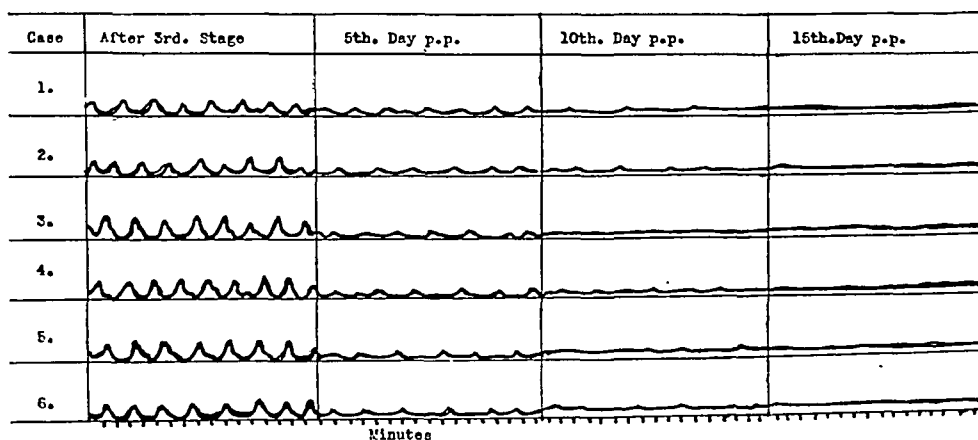


Fig. 1.—Contractions immediately after the third stage are high in amplitude, frequent, and have a long duration. On the fifth day they are greatly reduced in amplitude, rate, and duration. On the tenth day the uterus has lost most of its intrinsic motility and on the fifteenth day the uterus does not contract.

lasted about seventy seconds. On the fifth day the contractions were considerably reduced in amplitude; occurred somewhat more irregularly, every four to seven minutes; and had a much shorter duration, usually lasting thirty seconds or less. On the tenth day uterine motility was practically lost in all cases, there were no regular contractions, and the uteri were atonic. On the fifteenth day of the puerperium the uteri were absolutely nonmotile, contractions could not be elicited by increasing the pressure within the balloon nor by vigorous massage of the fundi.

It is interesting to recall that during pregnancy the estrogenic hormone is produced in an ever increasing amount until shortly before or at the onset of labor. The urinary titers of this hormone fall off abruptly after the delivery of the placenta. This would be expected in view of the fact that the placenta is by far the most efficient organ of estrin production. Woman is more nearly castrate in the midpuerperium, endocrinologically speaking, than at any other time during her reproductive life. This has been shown by studies on urinary estrin titers and biopsies of the vaginal epithelium. The progressively diminishing

## PUERPERAL UTERINE CONTRACTIONS\*

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CONTRACTIONS of the puerperal uterus are clinically important for two reasons: First and most important, the contractions of the myometrium are necessary for the prevention of hemorrhage; second, they have some interest in relation to after-pains. Immediately after the delivery of the placenta the open sinuses at the placental site are closed by this mechanism. Interlacing fibers of the myometrium act as an efficient means of controlling hemorrhage only when the muscle fibers contract. The physiologic mechanism operating to produce these rhythmic contractions in the post-partum period is not well understood. The pattern of diminishing uterine motility and diminishing response to oxytocics in the puerperium has been shown for the first time by this study. This study has also demonstrated the importance of one factor, estrogenic hormone stimulation, the presence of which is necessary for normal uterine contractions and normal oxytocic response in the puerperium.

### TECHNICAL PROCEDURE

Six normal primiparas have been studied after spontaneous labor at term and low forceps delivery. These patients received no amnesic or analgesic drug during labor, and they were delivered under novocain infiltration and pudendal nerve block. This was done in order to eliminate extrinsic factors which might interfere with the normal physiology of the puerperal uterus. In order to be absolutely certain that no external agent was introduced to confuse the results, epinephrine was not added to the novocain solution. The placenta was allowed to separate spontaneously in each case and was delivered by traction on the cord with the uterus held high in the abdomen. Immediately after delivery of the placenta the patient was redraped, the vagina thoroughly cleaned with tincture of metaphen through a large sterile speculum, the cervix exposed, and a rubber balloon of 100 c.c. capacity introduced by means of a uterine dressing forceps into the fundus. The balloon was attached to a cannula which connected by way of a rubber tube to the mechanical inkwriter. The mechanical inkwriter was so situated that contractions of the uterus were recorded on a revolving kymograph equipped with a timer. The balloon was then inflated with sterile water until pressure in the system was approximately 80 mm. of mercury. The capacity of the uterine cavity immediately after the third stage is 70 to 100 c.c. This capacity diminishes during the puerperium until on the fifteenth day the average capacity is 10 to 25 c.c. There was considerable difficulty in the first experiments because the uterus repeatedly expelled the balloon. This annoying dilemma was finally solved by using a toy

\*Read at the Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Atlanta, Ga., February 6 and 7, 1942.

the fall in blood estrin. Two patients (Cases 4 and 5) were given 1 mg. of estradiol benzoate (progynon B) daily on the fifteenth, sixteenth, seventeenth, and eighteenth days of the puerperium. Tracings taken on the eighteenth day show a good return of spontaneous contractions of the uterus (Fig. 3). The contractions are low in amplitude, occur every two to three minutes, and have a relatively short duration. The most significant recovery which resulted from the estrin therapy was demonstrated by the marked response to pituitrin which followed the estrin as compared with the total absence of response in the nontreated cases (Fig. 2). This observation is of real practical importance in relation to hemorrhage during the late puerperium. It would certainly seem wise in the light of these results to treat all hemorrhage after the fifth day post partum by first priming the uterus with estradiol and administering the oxytocic after the uterus has been resensitized. The administration of oxytocics is worthless after the tenth day. How long a time is required

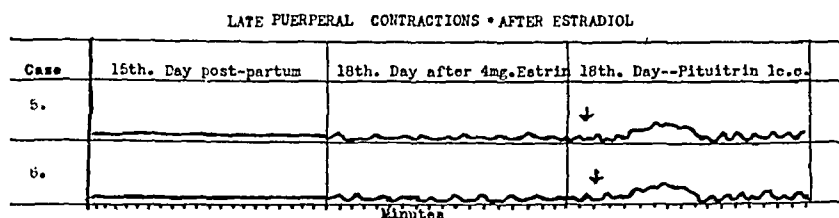


Fig. 3.—Uterus is quiet on the fifteenth day post partum; no intrinsic motility. After 1 mg. of estradiol benzoate for four days, intrinsic motility is restored and the uterus again becomes sensitive to pituitrin.

to resensitize a uterus with estrin in the late puerperium, I do not know but I fear that, with the natural estrogens, a minimum of twenty-four hours is required. In my experiments I arbitrarily took the tracing after four days of therapy. Perhaps diethystilbestrol may act more quickly.

#### CONCLUSIONS

1. Puerperal uterine contractions have been studied by means of an intrauterine balloon connected to a mechanical inkwriter which records the tracings of the contractions upon a revolving kymograph equipped with a timer.

2. The uterus rapidly loses its spontaneous contractions during the puerperium. After the tenth day no contractions occur. This loss parallels the drop in blood estrins.

3. Oxytocic response to pituitrin is rapidly lost during the puerperium. After the tenth day no response can be recorded.

4. A certain degree of intrinsic motility can be restored by the administration of estrin and the uterus is again sensitized to pituitrin. Puerperal hemorrhage after the fifth day should always be treated by estrin plus pituitrin.

uterine motility during the puerperium parallels the decline of the estrin titer in the blood, as this hormone is eliminated during the post-partum period. It would certainly seem logical to assume, in view of this observation, that the loss of intrinsic uterine motility as shown in the tracings was the result of the lack of estrin stimulation. This hypothesis, it is thought, may be strengthened by studies soon to be made relative to the return of uterine contractions and their relationship to endogenous estrin recovery. It will be shown in this report that intrinsic motility may be restored by the exogenous administration of estradiol benzoate.

#### OXYTOCICS IN THE PUERPERIUM

The same 6 patients in whom spontaneous contractions have just been described were given 1 c.c. of pituitrin subcutaneously immediately after the previous tracings were recorded. When the tracings were examined, it was noted that the response immediately after the third

#### PUERPERAL CONTRACTIONS • AFTER PITUITRIN

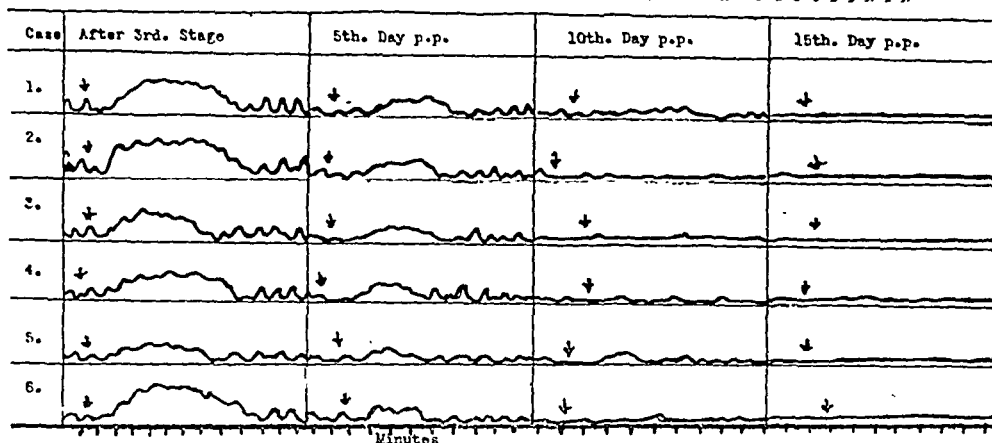


Fig. 2.—Arrows indicate point at which patients received 1 c.c. of pituitrin s.c. Note the marked oxytocic response immediately after the third stage, less response on the fifth day, no response in 4 patients and only slight response in 2 patients on the tenth day, and no response in any patient on the fifteenth day.

stage was marked. The uterus became tetanic within three to four minutes, and this tetany persisted for a variable length of time, in most cases about seven minutes. Perhaps even more significant than the tetany was the stimulation to more frequent contractions of a higher amplitude which followed the tetany. This secondary response was a most variable one, lasting in 1 case ten minutes and in another, over sixty minutes. On the fifth day the oxytocic response to pituitrin was reduced. There was moderate tetany followed by a period of hypermotility which lasted for a variable length of time. On the tenth day post partum, there was a very slight response to pituitrin in two cases followed by some motility but such response was absent in 4 cases. All of the cases failed to show any response on the fifteenth day. The uterus in the late puerperium loses its intrinsic motility and its ability to react to pituitrin (Fig. 2).

#### EFFECT OF ESTRADIOL BENZOATE

It may be assumed that the loss of uterine motility in the puerperium is the result of estrin depletion. The loss of uterine sensitivity parallels



Caldwell and Moloy's android pelvis in his classification, holding that this is not a true parent type, but represents an abnormal pelvis showing the effect of obscure growth or nutritional defects.

*Gynecoid*.—The pelvic inlet is circular or slightly flattened anteroposteriorly; its greatest transverse diameter passes through the central part of the anteroposterior diameter. There is a wide sacrosciatic notch, broad at the base and at the apex. The sacrum is backward in direction with a deep concavity. There is a wide subpubic angle and the pubic rami are short, giving a decreased depth to the pelvis.

*Android*.—The pelvic inlet is "heart shaped" so that the forepelvis is narrowed and the available space is diminished. The available space in the posterior pelvis is encroached upon by the exaggerated promontory. The greatest transverse diameter of the inlet is displaced posteriorly. The bore of the pelvis converges toward the outlet, the "funnel pelvis." The sacrosciatic notch is narrow at the apex, indicating a decreased bone length in the posterior iliac portion of the inlet. The sacrum is usually forward with a poor concavity. The subpubic angle is narrow and the pubic rami are lengthened giving an increased depth to the pelvis.

*Anthropoid*.—The inlet is relatively long anteroposteriorly and short transversely. The greatest transverse diameter is at the midpoint of the anteroposterior diameter. The direction of the sacrum is usually backward with a marked promontory and a shallow concavity. There may be moderate narrowing of the subpubic angle.

*Platypelloid*.—The anteroposterior diameter of the inlet is relatively shortened and the transverse diameter relatively widened. According to Thoms there must be a difference of 3 cm. or more to be so classified. The sacrosciatic notch appears narrowed; there is usually a wide subpubic angle.

#### TECHNIQUE

The technique of obtaining the anteroposterior diameter of the pelvic inlet by the four available methods requires further consideration: First, *the diagonal conjugate and the estimated true conjugate*. The details of obtaining this measurement require no explanation. It is customary to subtract 1.5 to 2 cm. from the diagonal conjugate to estimate the conjugata vera. Second, *the anteroposterior diameter of the pelvic inlet at operation*. At the time of abdominal operation, this diameter may be measured directly. The DeLee outlet pelvimeter is particularly suited for this purpose. The operator holds one arm of the pelvimeter against the promontory of the sacrum; his assistant places the other arm against the inner surface of the symphysis 1.5 cm. inferior to the superior margin. A reading is taken and recorded. For the purpose of eliminating the personal factor so far as possible, the operator and the assistant may reverse the manner in which the measurement is made and another reading recorded. Third, *the anteroposterior diameter* by means of x-rays directed perpendicular to the plane of the pelvic inlet.

The method is that of Thoms as modified by Torpin for speed and convenience. The patient is seated on the apparatus and the posterior marker set at the junction of the fourth and fifth lumbar vertebrae; the anterior marker is set at a point 1.5 cm. inferior to the superior margin of the symphysis. The patient is adjusted so that the two

## COMPARATIVE MEASUREMENTS OF THE FEMALE PELVIS\*

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RALEIGH, N. C.

THERE are four methods by which the diameters of the pelvis may be measured: (1) The diagonal conjugate may be obtained and the true conjugate estimated from it by subtracting 1.5 to 2 cm., (2) X-rays may be directed into the pelvic inlet by the technique of Thoms, Torpin, and others, (3) X-rays may be directed lateral to the pelvic inlet by the technique of Thoms, Jacobs and others, and finally, (4) the patient may be operated upon and the true conjugate measured directly.

Classification of the architecture of the pelvis is possible by the use of the x-ray. Several classifications are available. The more recent stem from the work of Turner and are based on morphology. Caldwell, Moloy, and Thoms have led in this work. They have borrowed extensively from the anthropologist, basing their classification on the contour of the pelvic inlet.

This study is undertaken with the purpose of comparing the antero-posterior diameters of the pelvis obtained by the four methods outlined above. Such a comparison should assist us in evaluating the meaning of the diagonal conjugate; it should further assist us in formulating an opinion as to the accuracy of x-ray pelvimetry. Furthermore, if in addition to diameters, the structure and contours of the birth canal are studied both by x-ray and physical means, we are aided in the clinical evaluation of the female pelvis.

### PELVIC CLASSIFICATION

#### CALDWELL AND MOLOY

Gynecoid  
Android  
Anthropoid  
Platypelloid  
Mixed forms  
Asymmetrical

#### THOMS

Mesatipellic  
Brachypellic  
Dolichopellic  
Platypellic  
Mixed forms  
Asymmetrical

The classification used is that of Caldwell and Moloy. The classification of Thoms is included for the purpose of clarity and comparison. It should be noted that Thoms uses the terms mesatipellic (round inlet) and brachypellic (transversely oval inlet) to describe Caldwell and Moloy's gynecoid pelvis. In the Thoms' system, the dolichopellic pelvis is the anthropoid pelvis of Caldwell and Moloy; the platypellic pelvis is obviously the same as the platypelloid pelvis. Thoms does not include

\*Presented at the Annual Meeting of the South Atlantic Society of Obstetricians and Gynecologists, Atlanta, Ga., February 7, 1942.

TABLE IA. SUMMARY OF STUDY

| PROCEDURE  | NO. CASES |
|--|-----------|
| Studied by x-ray pelvimetry  | 300       |
| Studied with both anteroposterior and lateral plates                               | 229       |
| No difference in true conjugate comparing anteroposterior and lateral x-ray plates | 191 (83%) |
| Studied digitally (diagonal conjugate)   | 222       |
| Measured at time of abdominal operation  | 44        |

TABLE IB.

| VARIATIONS IN GROUP   | CM.  |
|---|------|
| Average difference in true conjugate comparing anteroposterior and lateral x-ray plates | 0.34 |
| Shortest anteroposterior x-ray diameter   | 8.75 |
| Longest anteroposterior x-ray diameter  | 14.0 |
| Shortest x-ray transverse diameter  | 10.5 |
| Longest x-ray transverse diameter   | 15.0 |
| Longest diagonal conjugate  | 13.0 |
| Shortest diagonal conjugate   | 9.0  |
| Longest operative measurement   | 13.0 |
| Shortest operative measurement  | 8.0  |

It must be assumed that the most accurate method of measuring the anteroposterior diameter of the pelvis is the one actually made under direct vision at the time of abdominal operation. Comparison of these measurements with those made by x-ray should give an indication of the accuracy of the latter as a measuring device. As indicated in Table II, in 40 per cent of the cases measured by the first x-ray technique and in 41 per cent of the cases measured by the second x-ray technique, the operative and x-ray measurements were the same. This is not a high degree of accuracy. Dismissing for the purpose of discussion the errors due to faulty technique, the disagreement in the remaining 60 per cent of the cases may be explained on this basis; that the x-ray measures bone-to-bone only and any other technique, including the measurements made at the time of operation, is soft tissue-to-soft tissue measurement. We were frequently surprised at the amount of tissue lying on the inner

TABLE II. COMPARISON OPERATIVE MEASUREMENTS WITH ANTEROPOSTERIOR AND LATERAL X-RAY MEASUREMENTS IN 44 CASES

| A-P x-ray longer by   | 0<br>(equal) | 0.5-0.9<br>cm. | 1.0-1.4<br>cm. | 1.5-1.9<br>cm. | TOTAL |
|-----------------------|--------------|----------------|----------------|----------------|-------|
| Number of cases       | 18<br>(40%)  | 9              | 4              | 3              | 34    |
| A-P x-ray shorter by  | 0<br>cm.     | 0.5-0.9<br>cm. | 1.0-1.4<br>cm. | 1.5-1.9<br>cm. |       |
| Number of cases       |              | 5              | 4              | 1              | 10    |
| Lat. x-ray longer by  | 0<br>(equal) | 0.5-0.9<br>cm. | 1.0-1.4<br>cm. | 1.5-1.9        |       |
| Number of cases       | 17<br>(41%)  | 15             | 5              | 2              | 39    |
| Lat. x-ray shorter by | 0<br>cm.     | 0.5-0.9<br>cm. | 1.0-1.4<br>cm. | 1.5-1.9<br>cm. |       |
| Number of cases       |              |                | 2              |                | 2     |

markers are equal, since Caldwell has shown that a distortion of contour of the inlet may occur if the plane of the pelvic inlet is not at right angles to the center ray. An exposure is made according to the body structure and degree of pregnancy of the woman, and she is removed from the apparatus without disturbing the x-ray tube, markers, or plate. A lead grid perforated at centimeter intervals is placed on the markers and a flash exposure made. Fourth, *the anteroposterior diameter by means of x-rays directed lateral to the pelvic inlet.*

The method is that of Thoms and Jacobs modified by ourselves for speed and convenience. The patient stands with the right hip against the vertical table top, the left hip is directed toward the x-ray tube. She is adjusted so that she is at exact right angles to the center ray. The center ray is directed at a point 3 cm. below the anterosuperior iliac spine and at the center of the hip. An exposure is made according to the body structure and the degree of pregnancy. Before leaving this position the distance from the genital crease to the table top is measured. The patient is removed, the table is returned to the horizontal and the Torpin apparatus replaced. The markers are set at the distance measured from genital crease to table top minus one-half inch for thickness of the board. The lead grid is placed upon them and a flash exposure is made.

It is seen that by the use of the x-ray, two flat plates of the pelvis are obtained. The first, an anteroposterior picture, reveals the contour of the pelvic inlet; in addition to this a centimeter scale has been superimposed, permitting the reading of the diameters of the inlet. These diameters are read directly from the plate since the lead grid has been placed in the plane of the inlet and any distortion due to the x-ray is reproduced in equal amount in the centimeter markings on the plate.

The second, a lateral picture, reveals the architecture of the birth canal. From it the position, shape, and concavity of the sacrum, the contour of the sacrosciatic notch, and the depth of the pelvis may be seen. In addition, a corrected centimeter scale has been superimposed in the sagittal plane of the pelvis. The anteroposterior diameter of the pelvic inlet may be read from the grid markings (although not directly). An individual scale is made for each lateral plate, this applied to the film and the reading taken.

#### COMPARATIVE MEASUREMENTS AND CLASSIFICATION

In this study first, the anteroposterior diameter of one x-ray technique is checked for accuracy against the same diameter obtained by the second x-ray technique. Second, the anteroposterior diameter of the pelvis obtained by x-ray is checked for accuracy against the same diameter measured at the time of operation. Third, the anteroposterior diameter obtained by x-ray is compared with the diagonal conjugate. Fourth, the anteroposterior diameter measured at the time of operation is compared with the diagonal conjugate.

From a study of Table I it is seen that in 83 per cent of the cases the anteroposterior x-ray compared favorably with the lateral x-ray. The anteroposterior diameter was the same in both, allowing an error of 4 mm. This error seems acceptable since in our experience the same observer will not re-measure a diameter closer than that figure. Furthermore, two observers measuring the same diameter will vary as much as 4 mm. in their readings.

TABLE IV. COMPARISON DIAGONAL CONJUGATE WITH THE OPERATIVE MEASUREMENT IN 44 CASES

| Diag. Conj. greater by | 0<br>(equal) | 0.5-0.9<br>cm. | 1.0-1.9<br>cm. | 2 plus<br>cm. | TOTAL |
|------------------------|--------------|----------------|----------------|---------------|-------|
| Number of cases        | 14<br>(32%)  | 12<br>(27%)    | 8              | 2             | 36    |
| Diag. Conj. less by    | 0<br>cm.     | 0.5-2 plus cm. |                |               |       |
| Number of cases        | 0            | 8<br>(18%)     |                |               | 8     |

It is, therefore, seen that in this group the same conclusions are suggested: First, that in 77 per cent of the cases one is nearer correct in the clinical evaluation of the pelvis if the unmodified diagonal conjugate is accepted as the same as the true conjugate; second, that if 1.5 cm. were subtracted, one would have been right so far as the estimated true conjugate is concerned in 18 per cent of these cases only; third, that if 2 cm. were subtracted, one would have been right twice out of 44 times.

TABLE V. COMPARISON OF AVERAGES

| AVERAGE DIAMETER ENTIRE GROUP | CM.  |
|-------------------------------|------|
| Anteroposterior x-ray         | 11.5 |
| Transverse x-ray              | 12.6 |
| Diagonal conjugate            | 11.5 |
| Anteroposterior operative     | 11.2 |

Upon inspection of Table V, it is interesting to note that the same conclusions as those just outlined are indicated when one considers averages rather than actual diameters. It is seen that the average anteroposterior diameter by x-ray, the average true conjugate by actual measurement, and the average diagonal conjugate for this group are essentially the same measurement.

TABLE VI. CLASSIFICATION OF PELVES

| CLASSIFICATION AFTER CALDWELL AND MOLOY | NO. CASES | PER CENT |
|---|-----------|----------|
| Gynecoid                                | 222       | 74.0     |
| Android                                 | 4         | 1.33     |
| Anthropoid                              | 5         | 1.66     |
| Platypelloid                            | 5         | 1.66     |
| Mixed forms                             | 58        | 19.0     |
| Asymmetrical forms                      | 5         | 1.66     |

The classification (Table VI) of this "average pelvis" for the series is gynecoid. Its inlet would appear round to the eye, but upon actual measurement it would be slightly oval in the transverse direction. Seventy-four per cent of the pelves were gynecoid; 19 per cent were mixed forms. Concerning this latter classification, an explanation is necessary. A pelvis may be classified as mixed (for instance gynecoid-android) by which is meant that the posterior pelvis is gynecoid in structure and the forepelvis in android. In this series a pelvis was not classified as mixed unless the modifying factor was felt to be so marked as to influence the clinical course of labor.

surface of the symphysis. In support of this explanation is the further factor, seen in the table, that in the majority of these cases the x-ray measurement was longer than the corresponding measurement made at operation.

One is accustomed to subtract 1.5 to 2 cm. from the diagonal conjugate to obtain the true conjugate. A measurement so obtained is obviously not an accurate one since it is based on estimation. It seemed to us that by comparing the diagonal conjugate with the true conjugate, measured by x-ray and at the time of abdominal operation, some opinion as to the clinical value of this estimated true conjugate might be forthcoming.

TABLE III. COMPARISON DIAGONAL CONJUGATE WITH ANTEROPOSTERIOR AND LATERAL X-RAY MEASUREMENTS IN 222 CASES

| A-P x-ray longer by   | 0<br>(equal) | 0.5-0.9<br>cm. | 1.0-1.4<br>cm. | 1.5-1.9<br>cm. | 2 plus<br>cm. | TOTAL |
|-----------------------|--------------|----------------|----------------|----------------|---------------|-------|
| Number of cases       | 89<br>(40%)  | 58<br>(26%)    | 0              | 0              | 0             | 147   |
| A-P x-ray shorter by  | 0<br>cm.     | 0.5-0.9<br>cm. | 1.0-1.4<br>cm. | 1.5-1.9<br>cm. | 2 plus<br>cm. |       |
| Number of cases       | 0            | 43<br>(14%)    | 0              | 28             | 4             | 75    |
| Lat. x-ray longer by  | 0<br>(equal) | 0.5-0.9<br>cm. | 1.0-1.4<br>cm. | 1.5-1.9<br>cm. | 2 plus<br>cm. |       |
| Number of cases       | 64           | 59             | 0              | 0              | 0             | 123   |
| Lat. x-ray shorter by | 0<br>cm.     | 0.5-0.9<br>cm. | 1.0-1.9 cm.    |                |               |       |
| Number of cases       | 0            | 32             | 22             |                |               | 54    |

Attention is called to three facts in Table III comparing the diagonal conjugate and the x-ray true conjugate: (1) The fact that in 40 per cent of the cases the diagonal conjugate and the x-ray true conjugate were the same; (2) the fact that in 14 per cent of the cases the diagonal conjugate was greater than the x-ray true conjugate as would be anticipated, but that contrary to expectation this difference is neither 1.5 cm. nor 2 cm., but is less than 1 cm.; (3) the fact that in 26 per cent of the cases so compared the diagonal conjugate was actually less than the true conjugate. In this last group of cases, subtracting 1.5 to 2 cm. from the diagonal conjugate would not only fail to approximate the true conjugate, but would greatly increase the error already present in any estimated measurement.

So far as the clinical evaluation of the pelvis is concerned one would, therefore, seem nearer correct in 80 per cent of these cases if the unmodified diagonal conjugate were accepted as the same as the x-ray true conjugate. In this group of cases one would have been right in only 12 per cent of the cases if 1.5 cm. were subtracted from the diagonal conjugate; and right 4 times out of 222 if 2 cm. had been subtracted.

Similar conclusions are apparent when the diagonal conjugate is compared with the true conjugate measured at the time of abdominal operation (Table IV). Here the following facts, closely corresponding to the above, are found: (1) that in 32 per cent of the cases the diagonal conjugate measured digitally and the true conjugate measured at the time of operation are the same, (2) that in 27 per cent the diagonal conjugate is greater but by less than 1 cm., and (3) that in 18 per cent the diagonal conjugate was less than the true conjugate.

third and fourth days post partum, and the patient was discharged from the hospital in good condition on Jan. 15, 1941.

On the eighteenth day post partum, the patient telephoned that she was having cramplike uterine pains and also pain in the region of the appendix. When seen at home she exhibited no unusual symptoms except for a moderate tenderness over the uterus and in the area of the right ovary, and a slight increase in the lochia, which had previously almost stopped. She was given a course of ergotrate, and bed rest and heat to ovarian region were advised.

The following day she felt well, and remained so until the twenty-second post-partum day, Jan. 30, 1941, at which time she had a sudden massive hemorrhage, estimated at 1,500 c.c. The patient was immediately returned to the hospital and taken to the operating room within an hour of the hemorrhage. Exploration of the uterine cavity with the gloved finger revealed the entire cavity to be filled with tissue which had a rather firm, leathery feel, and which was densely adherent. Several small pieces of this tissue were removed by the gloved finger, and the diagnosis on frozen section, later by permanent section, was chorion-epithelioma.

At the time of removal of the above tissue, the patient became practically pulseless and in apparent shock. The uterus was quickly packed, and the patient was returned to her room. She responded well to general supportive measures. X-ray examination on Jan. 31, 1941, showed no involvement of the chest.

On Feb. 1, 1941, following a preoperative transfusion of 475 c.c. of citrated blood (the red blood count being 3,040,000 and the Hb 60 per cent prior to transfusion), a panhysterectomy was performed. The postoperative course was uneventful.

Sections from the uterus were diagnosed as syncytioma. Because of this variation in the report on the tissue removed from the uterine cavity, and that adherent in the uterine cavity, the specimen was taken to another pathologist who made independent sections and whose opinion was that the tissue showed no definite malignant changes, but merely obliteration of the uterine wall by pressure.

With this further confusion in the pathologic picture, it was felt advisable to secure still another opinion, principally because of the prognosis for the patient. Therefore, the specimen was sent to the pathology department of one of the nearby university medical schools. They sent a most complete and detailed report, which may be summarized by the following paragraph:

"It is our impression that differential diagnosis in this case rests between syncytial endometritis or placental polyp. It is our impression after review of the gross and microscopic findings that the picture is best described by the term placental polyp and represents retained placental tissue which has maintained its attachment to the uterine wall and with which it is incorporated. This process might be included by some under the first mentioned term, syncytial endometritis, though the lack of syncytial infiltration is against this designation. It is our impression, thus, that we are dealing with a persistence of placental elements with associated infection and necrosis and not with a tumor process."

#### COMMENT

In describing chorionepithelioma, DeLee<sup>2</sup> mentions that one of the many names by which it has been called is "invasive placental polyp."

## SUMMARY AND CONCLUSIONS

Since the use of x-ray in obstetrics, four methods are available for studying the anteroposterior diameters of the pelvis. A fair degree of accuracy is possible by x-ray methods; in addition, carefully made plates afford a satisfactory means of classifying the pelvis under study. It is necessary to emphasize, however, that the x-ray is not the answer to an obstetric problem in itself; nor is it an infallible instrument of precision; it is another means of study which when added to the usual pelvimetry, physical examination, laboratory studies, etc., assists us in obtaining the desired answer. When compared with the diagonal conjugate and the true conjugate, measured at the time of operation, it gives us a new insight into the value of the diagonal conjugate. In this series the unmodified diagonal conjugate appeared to be a more accurate measurement in indicating the true conjugate than the one from which 1.5 to 2 cm. has been subtracted. In the series of 300 women studied, the gynecoid pelvis was the predominating type; mixed forms were the next most frequent. The true "parent type" of pelvis is probably less often seen and the mixed forms more often seen than these statistics would indicate. Our qualifications for admission into the latter group may be responsible for this fact.

226 HILLSBORO STREET

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## PLACENTAL POLYP WITH SEVERE LATE PUERPERAL HEMORRHAGE\*

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HAGSTROM,<sup>1</sup> in May, 1940, reported a case of severe late puerperal hemorrhage due to placental polyp. He points out that the occurrence of such a condition is apparently infrequent, and bemoans the paucity of reports of such cases, both in obstetric textbooks and in the general literature.

The following case is presented because of its interest from the point of view of dangerous late hemorrhage and even more so because of the difficulty in differential diagnosis which causes the warning for a most careful pathologic examination to be made in any suspicious case.

### CASE REPORT

Mrs. L. R., a 23-year-old, white, gravida ii, para i, was delivered of her second baby at term on Jan. 8, 1941, the prenatal course and labor having been perfectly normal. Labor was of four hours and five minutes' duration. The placenta was delivered by modified Credé maneuver six minutes after the birth of the baby, and was apparently complete and intact. The blood loss was estimated at 150 c.c. The immediate puerperal recovery was uncomplicated except for an acute rhinitis in the

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\*Presented at the Fifth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Atlanta, Ga., February 6 and 7, 1942.



Due to three previous unsuccessful pregnancies, more than average precautions were taken to preserve this one. She was given lipolutin, one unit every five days, until the end of the fifth month, and thyroid extract,  $1\frac{1}{2}$  gr., daily throughout pregnancy.

Her pregnancy was uneventful until May 14, 1940, when the pelvic examination revealed an irregular mass presenting deep in the pelvis. Acute hydramnios was evident. The patient had gained a total of 36 pounds during pregnancy, six pounds during the last three weeks. Her blood pressure and urine had been normal.

*Roentgen Findings.*—Anencephaly with face presentation.

Labor began spontaneously on June 18, and thirteen hours later she was delivered of a dead fetus, presenting all the characteristics of anencephaly.

CASE 2.—Mrs. J. M., aged 32 years, para 0, gravida iii, had been married nine years. Her general health was good. Two spontaneous abortions occurred at three months during the past four years. Smith-Hodge pessary was inserted for temporary relief of a third-degree retroversion of the uterus on April 28, 1939.

Her last menstrual period occurred on Aug. 4, 1939. The expected date of confinement was June 11, 1940. General physical examination was negative. Uterus was held in position by the pessary.

Due to a long period of sterility and two unsuccessful pregnancies, this patient, likewise, was instructed to limit her activities a great deal more than in the average case. She was given corpus luteum, 1 c.c., every three days until the end of the fifth month. She was given thyroid extract, gr.  $\frac{1}{2}$ , twice daily. Her pregnancy was uneventful. She gained a total of 20 pounds. Her blood pressure and urinary findings were always negative. On May 5, she was found to have acute hydramnios. Upon vaginal examination no presenting part could be felt. Roentgen examination, due to the excessive amount of amniotic fluid, did not show the clear-cut detail desired. The presence of anencephaly was demonstrated with that part presenting at the pelvic inlet.

Labor began spontaneously on June 2 and, after twenty-seven hours, the patient was delivered by podalic version and extraction. The fetus, a typical anencephalus, was dead.

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Undoubtedly the dividing line between polyp and chorionepithelioma is in many cases very finely drawn, and it is the feeling of this author that a panhysterectomy should be immediately performed on such doubtful cases.

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2. DeLee, J. B.: *Principles and Practice of Obstetrics*, 1925, Philadelphia, W. B. Saunders Co.

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ANENCEPHALUS (WITH ACUTE HYDRAMNIOS)  
DIAGNOSED BY X-RAY\*

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NEWPORT NEWS, VA.

**A**NENCEPHALY is commonly associated with hydramnios. Clinically, this condition is rarely diagnosed before the onset of labor and more rarely before the rupture of the membranes. Roentgenography is a reliable means of demonstrating this anomaly long before it is possible to make the diagnosis by physical examination.

In our private practice, the discovery of two cases of anencephaly during the eighth month of pregnancy stimulated us to review the literature. We were surprised to find that only 31 cases had been reported. Harbeson<sup>1</sup> reviewed the literature in 1938, finding a total of 25 cases, to which he added one of his own. We were able to find 5 other cases, reported about the same time, which were not included in Harbeson's paper. These cases were distributed as follows: (1) Astier and Vernet<sup>2</sup> reported 2 cases in 1937, (2) H. Kuckens<sup>3</sup> 1 case in 1937, (3) Schubert<sup>4</sup> 1 case in 1937, and (4) S. G. Schenck<sup>5</sup> 1 case in 1940.

In all cases reported, where a reason was given for making the x-ray examination, it was one or all of the following: (1) Absence of the fetal head on clinical examination, (2) inability to determine the presentation and position by clinical examination, (3) acute hydramnios suggesting fetal anomaly. The x-ray findings in these cases were quite uniform, showing the absence of the bones of the calvarium and the bones at the base of the skull as an irregular mass, usually quadrangular in shape.

In our first case, x-ray examination was made because of the peculiarly shaped mass presenting in the pelvis, and because the patient had acute hydramnios. In our second case, in the presence of acute hydramnios, we were unable to feel a presenting part.

In reporting these two cases, we call your attention to the marked similarity in history and clinical course.

**CASE 1.**—Mrs. W. B. H., aged 30 years, para 0, gravida iv, had been married nine years. Her general health was good. Three abortions, at approximately two and one-half months, occurred during the past three years. The last menstrual period, Sept. 18, 1939. The expected date of confinement was June 25, 1940. Physical examination was essentially negative. All routine laboratory studies were negative except a basal metabolism rate of -12, and blood cholesterol 229 mg. per 100 c.c. of blood.

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these two groups of cases, 12 patients treated with female sex hormone and 12 treated with male sex hormone, a random group of 12 cases was chosen from the post-partum wards to serve as controls.

A generous biopsy specimen was taken from both walls of the uterine cavity of each of these patients, using a suction curette. At the same time, smears were taken from the vaginal epithelium. Only one patient was used to supply these simultaneous endometrial and vaginal specimens for any one day in the post-partum period. In this way, individual variations were minimized and yet a large group of patients could be sampled. One case from each group was followed beyond this twelve-day period, or until regeneration of the uterine mucosa was completed apart from the sex hormone effects (to be described). The cases were without complication and thus represented a good cross-section of the average post-partum patients.

The endometrial specimens were fixed in Bouin's solution and stained with hematoxylin-eosin. The vaginal smears were stained with acid fuchsin.

The dose of either estrogen or androgen was fixed arbitrarily at 10 mg. by mouth daily, for it represented about the average dose recommended for either suppression of lactation or as an aid in hastening involution.

This, then, gave three essentially similar groups of cases of 12 each, with more prolonged study in one case of each of the hormone-treated groups, one case in each group being followed until regeneration was complete. Individual variations are noted in the biopsy specimens, but the average trend remains of significance.

#### PATHOLOGIC DESCRIPTIONS

In a previous study I<sup>6</sup> followed the rate of the regeneration of the uterine mucosa in the normal post-partum patient, and studied the effect of lactation. Briefly, the endometrium was regenerated completely by twelve days post-partum, although the placental site was not cast off until six or seven weeks post partum, as Williams<sup>7</sup> demonstrated. Ovulation took place in the nonlactating post-partum patient on an average of six weeks post partum, with menstruation at eight weeks. Lactation arrested the endometrium in a repaired, resting phase, which persisted until lactation ceased. Occasionally, there would be evidence that the normal ovarian cycle would break through the pituitary inhibition of lactation, and that the patient would ovulate and menstruate while yet lactating; this latter is a well-known clinical fact.

Since this is reported in detail elsewhere,<sup>6</sup> only cursory mention will be made of this normal rate of regeneration as compared to the rate and order of regeneration in patients treated with the synthetic sex hormones as outlined. No significant departure from the usual picture is found in the first two days post partum of the hormone-treated cases, so description of these slides will not be given.

*Female Sex Hormone Influence, Endometrial Biopsies.*—These patients all had been given orally 10 mg. daily of diethylstilbestrol, and each day represents an individual case.

*Three-day post-partum specimen:* Vacuolated decidual cells with no definite evidence of involution, the cell outlines were somewhat indistinct. The gland epithelium was vacuolated with swelling of the

# CHANGES IN THE FEMALE GENITAL TRACT DURING THE PUERPERIUM INDUCED BY SEX HORMONE THERAPY

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THE ease with which modern therapeutists can prescribe constant, effective dosages of both synthetic male and female sex hormones has resulted in an ever-widening scope of clinical uses. Their employment has been most apparent in problems of abnormal uterine bleeding, failure of ovulation, sterility, ante-partum bleeding, or menopausal harassments. Sex hormone therapy in the postpartum phase has been limited to puerperal breast comfort<sup>1</sup> or to efforts to hasten involution of the uterus with resultant improvement in puerperal morbidity.<sup>2</sup>

The extensive literature which already has accumulated regarding the use of the estrogens and of the androgens in puerperal breast problems need not be reviewed. The majority of investigators feel that there is a definite place for such therapy, although the information regarding the side-effects of these agents is but slight. This paper will inquire into those changes.

Markee<sup>3</sup> noted the maintenance of good blood supply to the uterus using the estrogens. Wolf<sup>4</sup> and Falls, Lackner and Krohn<sup>5</sup> reported that the estrogens lend better tone to the post-partum uterus by increasing its contractility, and the former additionally noted that estrogens sensitize the myometrium to oxytocics. With this in mind, Connally and others<sup>2</sup> employed the estrogens in 200 cases in an effort to decrease post-partum morbidity. Five milligrams of diethylstilbestrol were given by mouth, beginning immediately after delivery, and were continued as a 5 mg. daily dose for the first twelve post-partum days. Morbidity (defined as a temperature of 100.4° F. for any two twenty-four-hour periods during the puerperium) was lowered from 12.8 per cent in a control series to 4.0 per cent in the estrogen-treated group. No untoward effects were noted, lochia was unchanged, and the rate of involution studied at twenty-one days post partum was thought to be hastened somewhat.

## MATERIAL AND METHODS

The cases selected for study were ward cases from the Boston Lying-in Hospital. These patients were not allowed to nurse because of still-born infants, previous breast abscess, or maternal disease. One series of 12 patients was given 10 mg. of diethylstilbestrol by mouth daily for the first twelve days post partum, the first dose being given immediately after delivery. A similar series of 12 patients was given 10 mg. of methyl testosterone by mouth, beginning immediately after delivery, and being continued for the first twelve days. For comparison with

specific in type, with no secretory activity. Both the stroma and glands resembled those of the basal endometrium.

*Twenty-seven-day post-partum specimen:* Rare mitoses in glands, with simple glands and nonspecific stroma. The picture was one of early proliferative endometrium.

Certain estrogen effects are evident from these slides. First and most notable effect is that the covering of the denuded endometrial cavity is accomplished by the ninth day under estrogen effect, whereas normally this is accomplished by the twelfth to thirteenth day. This might be anticipated because of the greatly increased mitotic activity

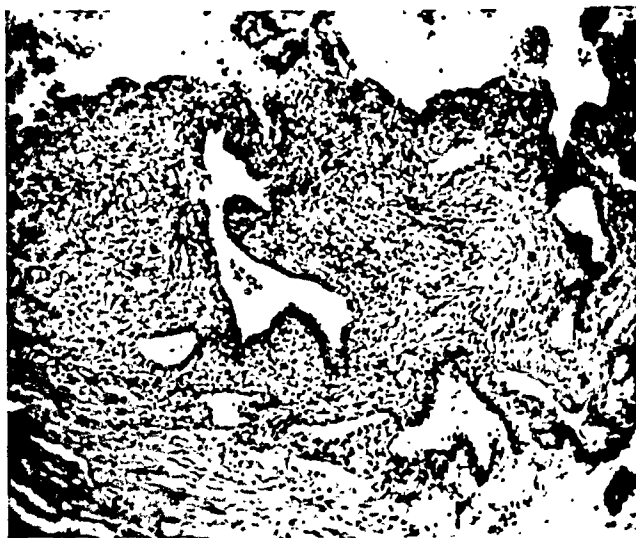


Fig. 1.—Normal nine-day post-partum endometrium. Epithelium is growing out from the gland stubs and has nearly completed the gap between glands. Stroma is non-specific basal in type. Glands are simple with cuboidal epithelium. Myometrium is well involuted.



Fig. 2.—Nine-day post-partum endometrium under female sex hormone influence. Epithelium has bridged the gap between the gland stubs. A mitotic figure is present in the surface epithelium. The stroma is predecidual in type. In other sections, gland epithelium has many mitotic figures with large nuclei, abundant cytoplasm. Myometrium as above.

nucleus; the stroma had slight infiltration of acute and chronic inflammatory cells; there was some trophoblast yet present.

*Four-day post-partum specimen:* Slough was present, the decidua was still well preserved as were the glands. The cytoplasm of each was swollen, less vacuolated, and the nuclei of both glandular epithelium and stroma were light staining and swollen. There were yet present some placental site syncytiotrophoblastic cells in the myometrium. Rare mitotic figures were seen in the glandular epithelium (they were seen first at this stage in the normal post-partum uterus<sup>6</sup>).

*Five-day post-partum specimen:* Slough was present; there were many mitotic figures present in the glands which were pseudostratified in type. The mitotic figures were in all phases and were much in excess of the normal post-partum five-day endometrium. The decidua still was well preserved, with the nuclei large and clear, looking almost like predecidua.

*Six-day post-partum specimen:* There was superficial necrosis; mitotic figures were marked in the glands with evidence of increased rate of regeneration. The stroma was both predecidual and decidual in type with large clear nuclei.

*Seven-day post-partum specimen:* Regeneration was still present within the glands, although fewer mitoses were seen. The stroma was of indifferent type, but was well maintained. There was some placental site trophoblast left.

*Eight-day post-partum specimen:* The glands were regenerating rapidly, with the endometrial surface being covered by epithelium growing out from the glands. Mitoses were frequent, the stroma was deciduallike in character. There was some evidence of chronic infection present.

*Nine-day post-partum specimen:* The surface now was covered completely by new epithelium from the glands which still showed excessive mitotic activity. The stroma was well maintained and was predecidual in type. The large clear nuclei of both the gland and stromal cells seemed to be characteristic. In the normal post-partum case, covering of the endometrial surface was not complete until twelve to thirteen days post partum.

*Ten-day post-partum specimen:* Here again was bridging epithelium, with the surface completely covered. The stroma was still predecidual in type, with a rare mitotic figure seen in the predecidual cells.

*Eleven-day post-partum specimen:* The surface was covered by adult epithelium. The stroma cells still were predecidual in type, more mitoses were seen, although they seemed to be losing some cytoplasm.

*Twelve-day post-partum specimen:* The glandular epithelium still showed evidence of mitotic activity, and occasional mitotic figures were seen in the surface epithelium of the endometrium. The stromal cells were predecidual, but were reverting now to a more basal type, with smaller, darker nuclei, and with less cytoplasm.

No more estrogen was given to one patient, who was followed nine days after withdrawal of hormone, and checked again fifteen days after withdrawal of hormone, or twenty-one and twenty-seven days post partum, respectively.

*Twenty-one-day post-partum specimen:* Mitotic figures still were present in the glands but were less numerous. The glands were non-

*Four-day post-partum specimen:* As above, only additionally, it was noted that the glandular epithelium had begun to change. There was slight swelling of the cytoplasm, the nuclei were pyknotic, and the cells themselves were somewhat irregular.

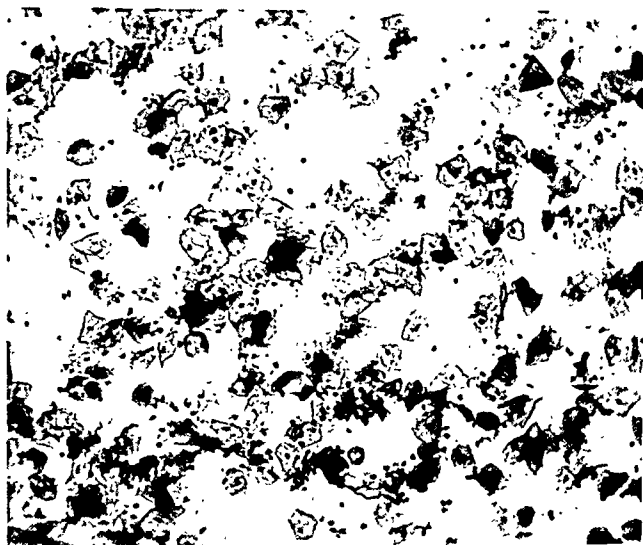


Fig. 4.—Normal ten-day post-partum vaginal smear. Abundant adult epithelial cells with small central nuclei, well-marked cytoplasmic margins, with only rare deep forms and but little debris.

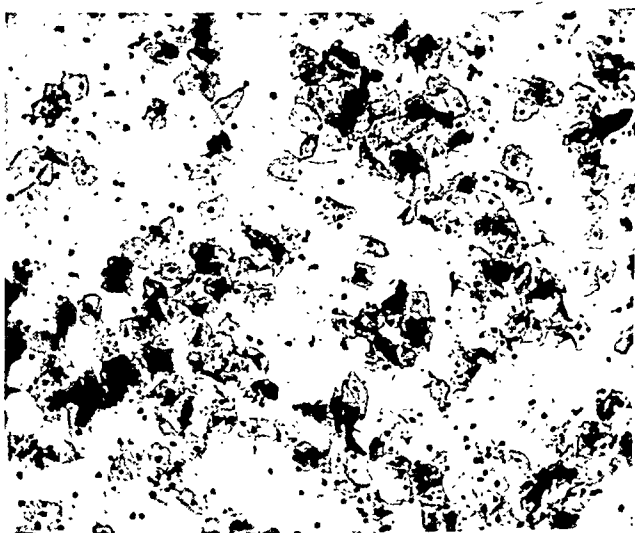


Fig. 5.—Ten-day post-partum vaginal smear under female sex hormone influence. Almost impossible to detect any difference between this smear and Fig. 4. Adult, well-delineated epithelial cells, little debris, with virtually no deep forms.

*Five-day post-partum specimen:* There were very little viable decidua left covering the myometrium, and there were a few glands left, with no mitoses present, and with the change noted above still present.

*Six-day post-partum specimen:* The glandular epithelium was cuboidal, much attenuated, with a rare mitotic figure present. The

throughout the entire endometrium, the glandular epithelium, the stromal cells, and even the surface epithelium as it grows outward. Mitotic figures are apparent in both the estrogen-treated group and in the normal post-partum group at four or five days in the glands, which re-cover the denuded surface by outgrowth of their epithelium.

Next of note is the fact that the stroma fails to return promptly to the nonspecific basal type seen in the normal post-partum group. The stroma is maintained as viable decidua or predecidua, in which under continued estrogen stimulation evidence of mitotic activity is seen. Ordinarily the post-partum decidua is sloughed as a superficial layer, with the deeper layer of spongy and basal decidua returning to the intermediate type of cell containing a small nucleus and relatively



Fig. 3.—Eleven-day post-partum endometrium under male sex hormone therapy. There is no evidence of epithelial activity, with bare myometrium in most areas. Glands are of simple cuboidal type with no mitotic activity. Myometrium involuting normally.

little cytoplasm. Such change did not take place here, but the decidua was maintained and even encouraged in proliferation by the estrogens. Promptly after estrogen withdrawal, the decidua regressed to its usual state, this being accomplished within eight days following estrogen withdrawal.

No change in myometrial regression was seen under estrogen effect. This was confirmed clinically as well by careful examination of uterine size at twelve days post partum. Involution grossly failed to differ from the normal.

Last of note is the absence of any evidence of infection or hemorrhage in this group of patients.

*Male Sex Hormone Influence, Endometrial Biopsies.*—These patients had been given orally 10 mg. daily of methyl testosterone, and each day represents an individual case.

*Three-day post-partum specimen:* There was little slough present, only a thin decidual layer, and burned-out glands were present. Recent thrombi were present in the vessels.



*Eighteen-day post-partum specimen:* Glands were simple and pseudo-stratified in type, with few mitoses. The epithelium was undergrowing the slough which still covered the surface. Rare mitoses were seen in the stroma which now resembled basal stroma. Hemosiderin was seen in macrophages in the stroma. (This patient used three or four pads daily for the first three weeks post partum.)

*Twenty-six-day post-partum specimen:* The surface still was not epithelized, mitoses were present, as was hemosiderin in some macrophages.

*Thirty-three-day post-partum specimen:* The surface was covered by simple epithelium, the glands were proliferative in type with occasional mitoses present, and the stroma was nonspecific in character.

Certain androgen effects were evident from these slides. First and most significant effect was that of marked retardation of repair of the endometrial surface. This was not accomplished for the first twelve days post partum under hormone therapy, and it was not until the hormone had been withdrawn from for two to three weeks that epithelial resurfacing was completed. This was in contrast with the usual process completed by the twelfth to thirteenth post-partum day. Mitotic activity appeared on the usual fifth day, but was of little significance throughout the period of hormone influence.

No change in myometrial involution was detected microscopically, nor on clinical measurements of gross uterine size.

In only one case of the 12 was there increased lochia. Three or four pads daily were used for the first twenty-one days. This is probably of little significance. No clinical evidence or microscopic evidence of infection was present. Evidence of old hemorrhage was seen in 2 of the cases.

*Vaginal Smears, Normal and Hormone-Treated.*—Numerous reports from various investigators have described changes in the vaginal epithelium which accompany cyclical endocrine phenomena. Smears of the vaginal epithelium were prepared in all three series of cases, the normal post-partum group, the estrogen- and the androgen-treated groups.

Smears prepared from the normal post-partum group were largely those of "full estrogen effect" with adult epithelial cells, rare deep cells or leucocytes. Daily variations in the essential pattern were minimal although on the sixth post-partum day there is a sudden definite increase in the number of deep cells, either of the navicular type or the small round cell type. This is noted from the sixth to the tenth day, following which the smear reverts to the normal full estrogen effect type, with adult cells of large distinct cytoplasmic margins and small centrally placed nuclei. From the picture presented in both the endometrium and in the vaginal smear, it would seem that regeneration of the endometrium is under estrogen control. Mitotic figures appear in the gland epithelium about the fifth day which may mark a sudden resurgence of circulating estrogen from ovarian activity. At about this same time, however, the vaginal smear shows a slight increase in number of less mature surface epithelial forms. This has disappeared by the tenth day, but it is at variance with the endometrial pattern of increased mitotic activity present in the glands. However, it may be that the vaginal mucosa is a less sensitive instrument recording hormone variations, and that the relatively complete estrogen effect seen during the first four post-partum days is a carry-over from the higher

stroma was nonspecific in type, extremely thin, and no decidua were recognizable except through the slough.

*Seven-day post-partum specimen:* The glandular epithelium was cuboidal, with nuclei which seemed large, clear, with swollen cytoplasm. The stroma was regressing and indifferent in type.

*Eight-day post-partum specimen:* There seemed to be no effort to cover the denuded myometrium. Only a scanty, resting stroma covered the myometrium. Infrequent glands were seen with pale, swollen nuclei; only a rare mitosis was present. A patch of involuting decidua still was present in this patient.

*Nine-day post-partum specimen:* Some effort to recover the surface was seen here, with simple epithelium growing out to cover partially the surface. Slough was present, with old hemorrhage. Both glandular epithelium and stroma were of simple resting type.

*Ten-day post-partum specimen:* There was virtually nothing covering the myometrium, yet there was no evidence of hemorrhage or infection.

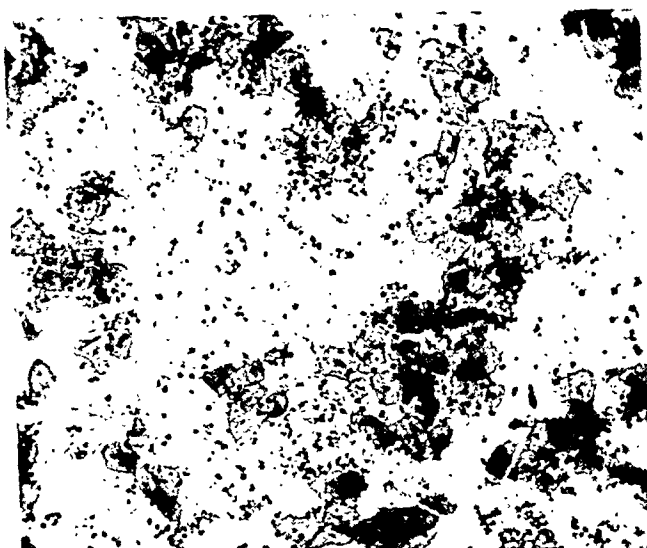


Fig. 6.—Ten-day post-partum vaginal smear under male sex hormone influence. Less florid smear, with many adult forms, but as well many less mature forms with larger nuclei, less cytoplasm. Some "boat-shaped" or navicular forms. Much more debris than in previous smears. This smear is suggestive of the partial castrate smear.

*Eleven-day post-partum specimen:* Only a few burned-out glands were present, usually as small nests of epithelium down in the myometrium, with rare mitoses. Stroma was nonspecific, greatly thinned out or absent in patches. There was no mitotic activity in the stroma, and no evidence of recovering of the surface to which were adherent fibrin, leucocytes, and slough.

*Twelve-day post-partum specimen:* No more effort was seen in covering the denuded surface. The gland stubs stop short at the myometrial surface, which in some areas was covered with but a few layers of basal-type stroma.

One patient was followed six, fourteen, and twenty-one days following withdrawal of the male sex hormone, or on the eighteenth, twenty-sixth, and thirty-third post-partum days.

patient is not lactating, ovulation occurs on the average at six weeks, with menstruation some fourteen days later.

The efficiency with which this natural process is consummated is common knowledge. Only the rare case requires medical aid. However, under estrogen treatment the process of involution seems retarded, for the glands are maintained at a high level and under forced draft re-epithelize the mucosal surface by the eighth or the ninth day; some 25 per cent quicker than is normal. Mitotic activity is greatly increased in the glandular epithelium. The stroma is not allowed to involute, but is maintained as decidua or as predecidua, with actual proliferation induced in these cells as evidenced by mitotic activity. The swollen cytoplasm, large clear nuclei, and mitotic figures present in both these elements are unmistakable. It may be suggested that the basal zone of endometrium is the last to change into decidua and is the quickest zone to regress after pregnancy is terminated. Under estrogen stimulation, this zone may not be allowed to regress, but proliferation is forced while it is still in its predecidual or decidual phase. Many variations are noted under estrogen treatment, from the bare nuclei of undifferentiated stroma to predecidua or decidua. Each patient is to be allowed her individual variations, but the general trend is unmistakable.

After estrogen is withdrawn, glandular and surface epithelial activity shades off as it normally does. However, a full week is necessary before the stroma regresses from its decidual form into the basal type. The more rapid covering of the denuded endometrium clinically may have lowered the incidence of post-partum morbidity.<sup>2</sup> Whether the stimulus given by estrogens to epithelial activity is dangerous is a difficult question, had the patient retained trophoblastic tissues, or had abnormal trophoblastic tissue been present and viable.

Under androgen therapy, the process of decidual involution is unchanged, but repair is brought almost to a standstill. Effort to resurface the denuded myometrium is alarmingly slight, and but little is made until the androgen is withdrawn. Three weeks after withdrawal, the surface is epithelized, but during this period resistance of the endometrium to infection may be lessened and the possibility of bleeding may be greater.

Under neither agent, however, was myometrial regression affected, either on the basis of clinical or microscopic evidence.

#### SUMMARY AND CONCLUSIONS

1. Three different groups consisting of 12 patients each were studied by endometrial biopsy and vaginal smear during the puerperium. One group was normal post-partum patients and each supplied a single day's picture. A second group of normal post-partum patients was given 10 mg. of diethylstilbestrol orally for the first twelve post-partum days, each patient giving only one endometrial biopsy and one vaginal

estrogen levels of pregnancy. As these influences are withdrawn, some five days later a florid desquamation takes place with the appearance of a slightly increased number of deeper cell forms. Following this, the less sensitive vaginal epithelium slowly returns to full estrogen effect from ovarian sources although this may not be complete until ten days post partum. Whatever the interpretation, nevertheless, it may be said that the vaginal epithelium normally presents the picture of a mature, resisting epithelial surface.

Under the influence of 10 mg. of diethylstilbestrol daily, orally, for the first twelve days, the vaginal epithelium consistently shows full estrogen effect, without the tendency noted above for a slight drop in adult forms. It is extremely difficult to tell the difference between the normal post-partum smears and the smears from the estrogen-treated group unless there possibly is a little less debris, a few less deep forms and leucocytes. This is noted consistently from the immediate post-partum smear onward. No therapeutic conclusions can be drawn.

Under the influence of 10 mg. of methyl testosterone daily, orally, for the first twelve days post partum, the vaginal epithelium resembles that of the normal post partum until the fifth or sixth day when there is a definite increase in the number of less mature forms and deep cells, and more leucocytes. This coincides with the appearance normally of these forms, and lends support to the impression that the vaginal epithelium is a less sensitive end organ for hormones than the endometrial tissues. The full estrogen effect of pregnancy is pictured by the vaginal epithelium for five or six days after it is withdrawn. Male sex hormone in the magnitude used in this study does not change this process, but as the deep forms appear normally, male sex hormone exaggerates the continuance and quantity of the less mature forms. This change is not seen in the patients under estrogen treatment. As the male sex hormone is continued, the smear comes to look more and more like that of testosterone effect or of partial castration. It never fully approaches the smear of a complete castrate or postmenopausal patient.

Within a week after male sex hormone is withdrawn, the vaginal smear is again that of full estrogen effect and continues so thereafter. No change from the normal is seen in estrogen-treated cases followed for some weeks. Practically, there is no apparent therapeutic significance in these findings, for repair of episiotomy incisions or vaginal lacerations proceeds at the average rate. Photomicrographs have been prepared demonstrating the appearance of the vaginal smear at ten days post partum in the normal and in the hormone-treated series.

#### DISCUSSION

If one breaks down into sequence the physiologic changes by which the post-partum endometrium is returned to the nonpregnant endometrium, three phases are noted: involution, repair, and regeneration. Normally, involution is completed within the first four or five days, repair occupies the next six or seven days with appearance here of mitotic activity, and regeneration proceeds from thence onward.<sup>6</sup> If the patient is lactating, the endometrium remains in the completely regenerated, resting phase until ovulation ensues either while the patient is still lactating, or after this function has concluded. If the

# CLINICAL EXPERIMENTS IN RELATION TO THE EXCRETION OF THE ESTROGENS\*

## II. FUNCTIONAL FLOWING. URINARY ESTROGENS BEFORE, DURING, AND AFTER PROGESTERONE, ESTRIOL, AND CYCLIC ADMINISTRATION OF PROGESTERONE AND ESTRADIOL BENZOATE

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### INTRODUCTION

THE patient upon whom these studies were made began having functional flowing in 1930, three months after the onset of menstruation at the age of 15. Curettage had been performed twice before she came to the Free Hospital for Women in January, 1934. No organic disturbance except abnormal uterine bleeding and secondary anemia has been discoverable during the eight years that she has been cooperating with us in attempts to cure her disability by conservative measures. Seven times, through January, 1938, have specimens of endometrium showed marked hyperplasia.

She has taken large quantities of ferrous sulfate for anemia. Estrogens, chorionic gonadotropin, progesterone (in amounts which we now recognize as inadequate), wheat germ oil, anterior pituitary extract, and oral placental extract (Eley) have been tried and repeated with little or no discernible therapeutic effect on her bleeding, which has duplicated every pattern of functional flowing.

In July, 1934, curettage, resection of a 3 cm. thecal luteal cyst of the left ovary, appendectomy, and uterine suspension were performed. Nearly four months of amenorrhea ensued. Intrauterine application of well-screened radium, 300 mg. hours, given in April, 1935, for recurrent bleeding, was followed by amenorrhea of six months' duration, and then a recurrence of the disorder in the form of irregularly occurring, prolonged spells of staining without excessive loss of blood. The patient married in June, 1936.

Urinary estrogens were measured in January, 1938, before; during, and after the parenteral administration of fairly large doses of progesterone and estrone. This study has been reported.<sup>6†</sup> Thereafter came four months of amenorrhea and then intermittent staining interspersed with one- to ten-day spurts of flowing.

\*Presented in brief before the New York Obstetrical Society on January 13, 1942.

The Mrs. William Lowell Putnam Investigation of the Toxemias of Pregnancy, aided by grants from the Committee on Research in Problems of Sex of the National Research Council.

†All references will accompany the fourth paper of this series.

smear. A third group of normal post-partum patients were given 10 mg. of methyl testosterone orally for the first twelve post-partum days, each patient giving only one endometrial biopsy and one vaginal smear.

2. These hormone-treated patients demonstrated definite variations from the normal processes of involution, repair, and regeneration.

3. Involution was delayed by female sex hormone, but not by male sex hormone.

4. Repair was hastened by female sex hormone, but markedly retarded by male sex hormone.

5. Regeneration was hastened for covering of the surface epithelium by female sex hormone, but stromal regeneration was delayed. Regeneration was delayed by male sex hormone.

6. The effects of female sex hormone were lost within one week after withdrawal, and the effects of male sex hormone were lost within three weeks after withdrawal of the hormone.

7. Certain theoretical questions regarding the use of either agent in the puerperium are raised.

Acknowledgment is made to Dr. Arthur T. Hertig and to Dr. Frederick C. Irving, for critical review of this paper. The following are thanked for their experimental grants of the following: E. 391 (oral), diethylstilbestrol, Department of Medical Research, Winthrop Chemical Co. Oretone—M (oral), Methyl testosterone, Schering Corporation, Dr. Max Gilbert, Mr. R. W. St. Clair, the latter of whom supplied the excellent photomicrographs. Metandren (oral) methyl testosterone, Ciba Pharmaceutical Products, Mr. E. O. Paden.

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Ishmael, William K.: *Menopausal Arthralgia*, *J. Lab. & Clin. Med.* 27: 297, 1941.

The diagnosis of menopausal arthralgia can be made only if rheumatic symptoms dating back to the age of the menopause completely yield to appropriate treatment.

In the fairly large series reported by Ishmael, he applied as general supportive measures: diet, avoidance of trauma, avoidance of unfavorable climatic factors, leaving foci of infections intact, administering supplementary vitamins, correction of disturbances of metabolism, of gastrointestinal function, of emotion, posture, etc., and finally relief of pain. Added as specific measures are: estrogenic substances, autohemotherapy, and artificial fever. He also made use of physical therapy and orthopedic measures.

Analyzing his results he concludes that stilbestrol should preferably supplant the use of the estrogenic hormone.

HUGO EHRENFEST.

assays of crystalline estradiol, estrone, and estriol. Twenty-four- to forty-eight-hour specimens were extracted, but all results are expressed in terms of twenty-four-hour excretion for the sake of comparison.

Bleeding necessitated the use of a retention catheter for collecting urine. Absence of estrone, a high percentage of activity in the estradiol fraction, and a marked increase in the estrogenic potency after zinc-hydrochloric acid hydrolysis featured the control specimen. This is the typical partition of urinary estrogens at the time of menstruation, both normal and abnormal. To us these findings reflect more rapid degradation of estrogens and restricted estradiol to estrone to estriol conversion, these processes in turn reflecting reduced or absent steroids of the progesterone type.

Specific treatment with really adequate amounts of progesterone\* retarded and finally stopped the flow. No change in the total estrogenic potency acquired by simple hydrochloric acid hydrolysis of the urine resulted but in terms of weight two to three times as much estrogenic substance was excreted, the reason being that progesterone caused conversion of the more active estradiol to less active estrone and estriol and retarded degradation, as further indicated by the reduction of the "unaccounted for" potency after zinc-hydrochloric acid hydrolysis. Since estrone is the most labile of the known estrogens, its appearance was still further evidence that progesterone had depressed the degradation mechanism. These results confirm previously reported findings on this same patient<sup>6</sup> by providing direct evidence for the role played by progesterone in decreasing the rate of estrogen degradation and facilitating estradiol to estrone to estriol conversion.

Sixty hours after the last injection a profuse progesterone-withdrawal period began, on the second day of which the amounts and partition of the urinary estrogens were essentially similar to those before treatment. Fifteen days later, eleven days after the end of the period, the only significant change in the urine was the reduced values indicating reduced ovarian activity.

#### A TRIAL OF ESTRIOL ORALLY (CHART 2)

Our object in this study was to put the ovaries at rest temporarily in the hope that a return to normal function would ensue. Estriol† was chosen because we desired to learn more about its fate after ingestion. It was taken in alcoholic solution from Dec. 20, 1940, through March 14, 1941, the daily dose being increased from 0.5 to 1.0 mg. on January 20 and to 2.0 mg. on March 4.

Good absorption and, compared with estrone and estradiol, considerably less destruction are indicated by the urinary recovery of 24 to 37 per cent. Similar recoveries of orally administered estriol have been obtained in three other patients. Such relatively high recovery is in keeping with its known greater stability. Furthermore, the  $T_{zn}$  to  $T_o$  ratios during treatment are the lowest we have ever found in this patient and signify to us that the degradation process was being retarded, not only because of the stability of estriol but also possibly because of the

\*Proluton, a product of the Schering Corporation.

†Theclol, a product of Parke, Davis & Company, through the courtesy of Dr. E. A. Sharp.

Although the basal metabolic rate was normal, thyroid extract, one-half a grain three times a day, was prescribed and taken faithfully from November, 1938, through September, 1941. From March through November, 1939, the patient had periods, at twenty-seven- to thirty-six-day intervals, varying from a day of staining to six days of profuse flow. After two months of amenorrhea and a month of staining, came a profuse flow and then three episodes of staining at thirty-three- to thirty-five-day intervals. Increasingly profuse flow starting in August, 1940, brought the patient to the hospital late in November, 1940, at the age of 25, when the studies and therapies herein reported were begun. At that time her hemoglobin was 42 per cent by the Sahli method.

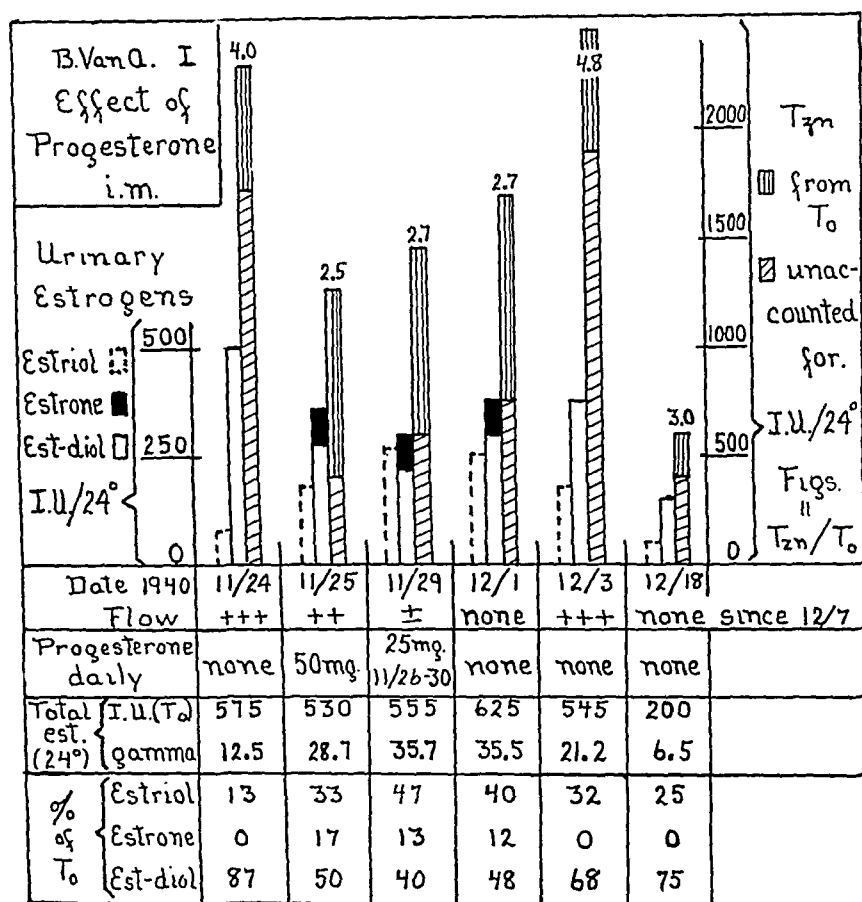


Chart 1.

## THERAPY WITH PROGESTERONE ALONE (CHART 1)

For the methods of urinalysis employed and for explanation of the charts, the reader is referred to the first paper of this series. "Unaccounted for"  $T_{zn}$ , that is, the estrogenic activity of urine after zinc-hydrochloric acid hydrolysis which cannot be accounted to the estrogens already present, as well as  $T_{zn}$  to  $T_0$  ratios appear to provide considerable information concerning estrogen destruction. Total urinary estrogens are expressed both in activity units (I.U.) and by weight (micrograms), the latter being calculated on the basis of standardization



tion, indicating increased ovarian activity, and a continued rise in  $T_{zn}$  to  $T_0$  ratios, evidence for more estrogen breakdown, there was a drop in the amount of "unaccounted for"  $T_{zn}$  potency. This suggests that during estriol medication at least part of the "unaccounted for" value came from reactivation of estrogenically inactive estriol metabolites. One might interpret the steady increment in  $T_{zn}$  activity during the latter part of the period of medication, therefore, as indicating that continued and increasing dosage of estriol, although not affecting the recovery of estriol as such, resulted in less complete degradation so that a larger percentage of inactive estriol metabolites could be reactivated.

Although the evidence after cessation of estriol ingestion points to more ovarian activity and therefore to a certain amount of ovarian inhibition during therapy, the presence of urinary estradiol during the medication period in amounts above the control and the patient's continued functional flowing show that the object of the experiment, complete ovarian inhibition, was never accomplished.

We have since discovered that the daily ingestion of 2.5 mg. of estriol failed to affect the cycles of a sterile patient and that 1 to 5 mg. daily for three and one-half months failed to affect the cycles or pain of another patient with essential dysmenorrhea. When this last patient, however, took 15 mg. of estriol daily starting on the fourteenth day of the cycle, menstruation was forestalled until the fortieth day, two days after the last dose.\* Biddulph and his associates,<sup>14</sup> working with parabiotic rats, have shown that sixty times as much estriol is required to suppress the castrate pituitary as estradiol. We wonder whether the comparative ineffectiveness of estriol in influencing pituitary-ovarian activity may not be related to the greater resistance of this estrogen to degradation in the body. We have stated our reasons<sup>8</sup> for believing that the pituitary-ovarian effects of estrogen may be accountable to degradation metabolites rather than to estrogens themselves.

Because the patient's excessive bleeding which started on April 6 showed no sign of letting up, progesterone, 25 mg., was given daily from April 9 through April 13, inclusive. Flowing decreased but did not completely stop during injections. Profuse flow started again two days after the last injection and ceased entirely five days later.

#### CYCLIC ADMINISTRATION OF PROGESTERONE AND ESTRADIOL BENZOATE (CHARTS 3 AND 4)

Although withdrawal bleeding may be produced in both monkeys and women with estrogens alone, it is becoming increasingly apparent that progesterone is a very much more effective agent than the estrogens in the control of endometrial flow.<sup>15-17</sup> In our own experience and that of others, it has been noted that, whereas estrogen withdrawal may result in anything from no flow at all to prolonged and uncontrolled bleeding, progesterone and estrogen withdrawal is almost invariably followed by an amount and type of flow which parallel the normal catamenia. Since animal investigation and our own studies on women<sup>6-10</sup> have shown that

\*This period was more profuse and much less painful than usual. It would appear that the luteal phase of the cycle was prolonged by this large daily dose of estriol. The consequent symptomatic relief is in keeping with the hormonal findings on this patient which are reported in the third paper of this series.

greater quantity of steroid present. In view of this evidence for decreased destruction, the failure to find any estrone in these specimens shows that estradiol to estrone conversion was being prevented. Though contrary to our thesis concerning the favorable effect of decreased destruction upon conversion, prevention of conversion in this instance would be expected according to the law of mass action since the concentration of the end product of the estradiol to estrone to estriol reaction was raised. Also, since there was a decrease in excreted estradiol during the first six weeks of the experiment and no later increase commensurate with the augmentation of estriol, it appears that neither estrone nor estradiol is formed from estriol, as was shown in earlier work on rabbits.<sup>12, 13</sup>

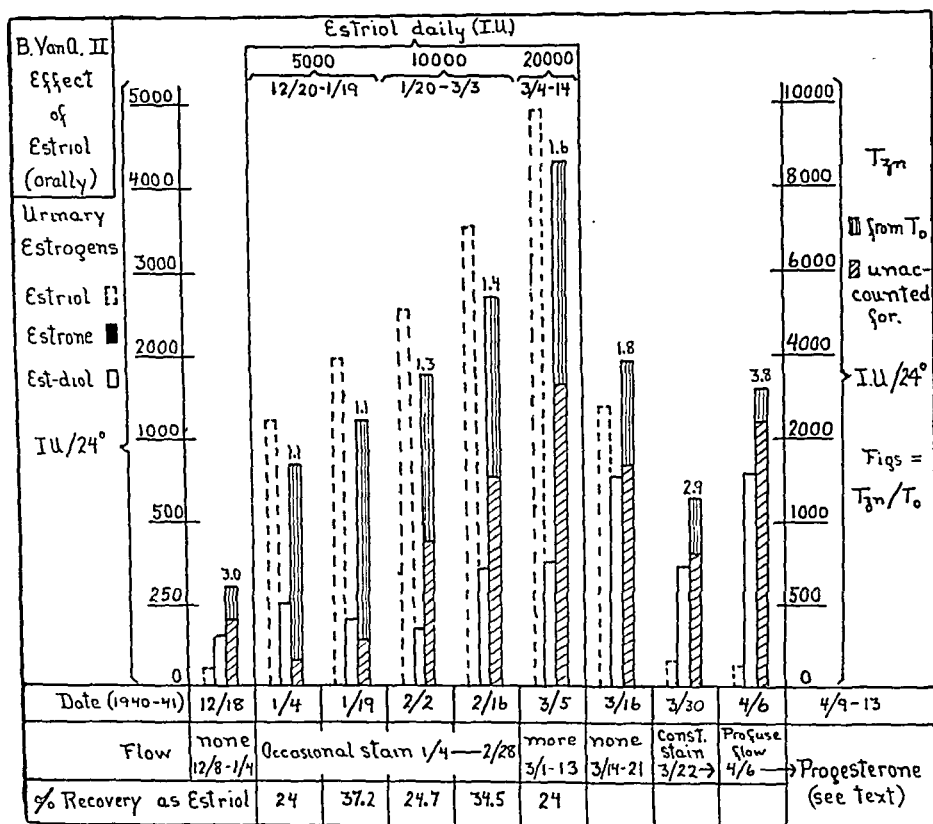


Chart 2.

A constant increment, after the first month of estriol medication, may be noted both in the  $T_{zn}$  to  $T_0$  ratio and in the amount of "unaccounted for" activity after zinc-hydrochloric acid hydrolysis. Two interpretations of this observation are possible. The fact that this increment was associated with an increased excretion of estradiol (presumably the primary ovarian hormone) suggests that, despite the larger dosages of estriol, greater ovarian secretion was taking place at this time. On this basis the higher  $T_{zn}$  to  $T_0$  ratios and greater amounts of "unaccounted for"  $T_{zn}$  activity may have come from estradiol breakdown products. On the other hand, although cessation of estriol administration was followed by a considerable augmentation of estradiol excre-

started on June 20, six days after the last injection. This procedure was repeated exactly in July and August, each series of injections being started on the twenty-second day from the start of the last period and resulting in normal flow six days after the last injection. In September the same timing of injections was adhered to, but twice as much estradiol benzoate was given. This was followed by a twelve-day interval between the last injection and the start of flow, making a thirty-eight-day interval between catamenia rather than the thirty-one-day intervals

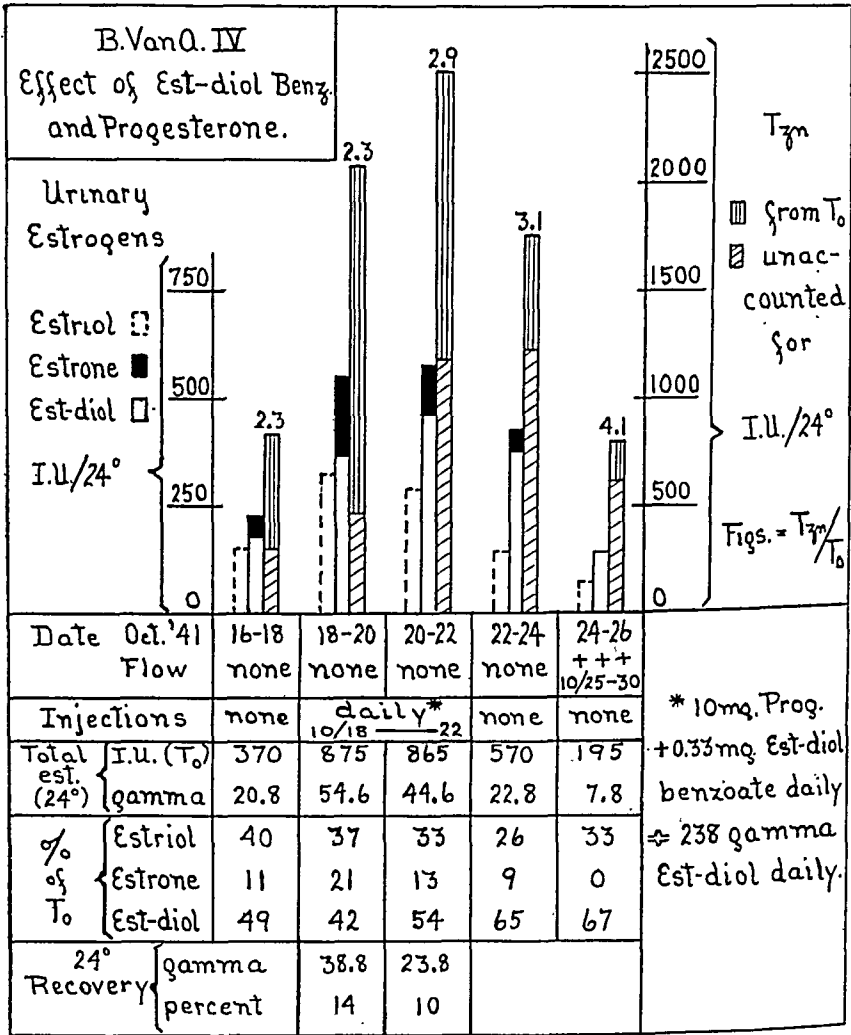


Chart 4.

which had resulted from the three previous cycles of therapy. It seems apparent that estrogen overdosage prolonged the interval between injections and withdrawal bleeding. The seventh and last series of injections, 10 mg. of progesterone and 0.33 mg. of estradiol benzoate daily for five days, was started on Oct. 18, 1941, the twenty-second day since the start of the September period. A five-day period began on October 25, three days after the last injection, making a twenty-eight-day interval between catamenia.

estrogen is necessary for the optimum effect of progesterone, the administration of estrogen together with progesterone in cases of progestin deficiency is rational, and has indeed been found<sup>10, 16, 17</sup> to augment the effectiveness of progesterone therapy. Because of the above considerations and because of the known retroactive effect of ovarian secretions upon the pituitary, it was decided to produce cyclic estrogen and progestin-withdrawal bleeding in this individual, in the hope not only of controlling her abnormal flow but of establishing a normal cyclic pituitary-ovarian relationship which would continue after cessation of the artificially-produced condition. This form of therapy in functional

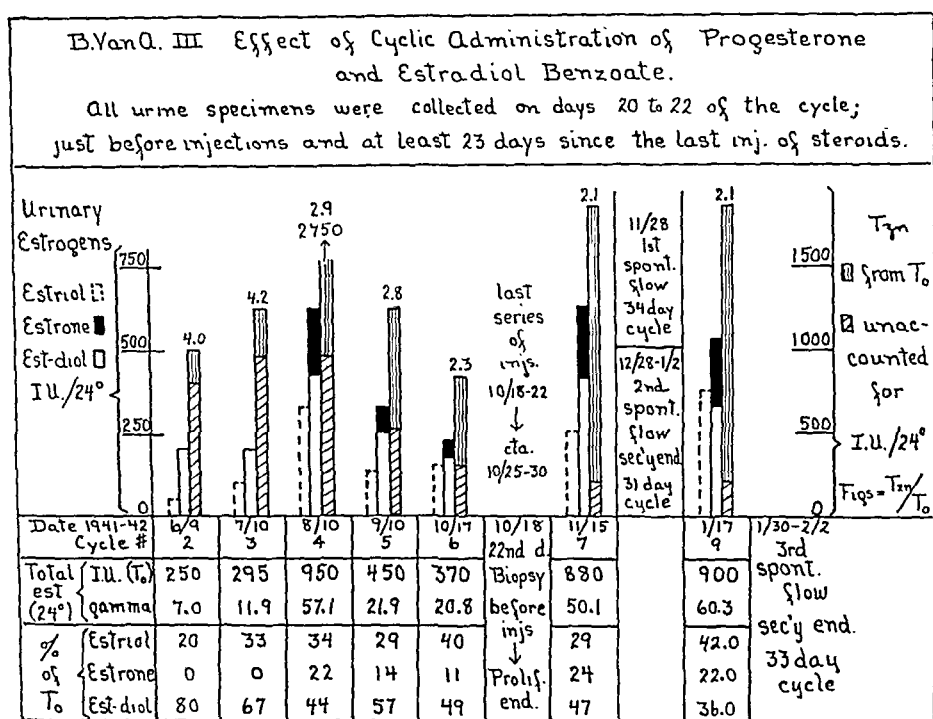


Chart 3.

flowing has already been reported upon favorably by Hamblen.<sup>17</sup> We were particularly interested in determining whether or not any resultant spontaneous ovarian control would be reflected in a more normal metabolism of the ovarian steroids as gauged by the urinary metabolites.

On May 5, twenty days from the start of the April progesterone-withdrawal period, 10 mg. of progesterone and 1.25 mg. of estradiol benzoate\* were given intramuscularly, this dosage being repeated for five consecutive days. On May 19, ten days after the last injection, a normal five-day period began. It was decided, because of the prolonged interval between injections and the start of flow, that less estrogen should be administered. Beginning on June 10, therefore, twenty-two days from the start of the previous flow, five daily doses of 10 mg. of progesterone and 0.33 mg. of estradiol benzoate were injected. Withdrawal flow

\*Proluton and Progynon-B, supplied by the Schering Corporation.

complete conversion and the least destruction of secreted estrogen that we have ever found in this individual. Even when 50 mg. of progesterone were given (see November 26, 1941, Chart 1), there was a higher percentage of activity in the estradiol fraction and less in the estrone, and the recovery of "unaccounted for" activity after zinc-hydrochloric acid hydrolysis was greater. One might surmise that during the luteal phase of an ovulatory cycle this patient's ovaries secrete more than 50 mg. of progesterone in twenty-four hours.

In Chart 4 are presented the results of urinalyses during the last estrogen and progesterone treatment. All urine passed from forty-eight hours before the first injection through the ninety-sixth hour after the last injection was saved in forty-eight-hour batches. Menstruation started eighty hours after the last injection.

The recovery of the injected estradiol is approximated by using the control specimen as the base line and assuming that the benzoate ester was broken down in the body into a corresponding weight of  $\alpha$  estradiol. The figures indicate that  $\alpha$  estradiol, even in the presence of fairly large amounts of progesterone, is more rapidly destroyed than is estriol (see Chart 2). Its recovery, however, is four to five times as great as that of estrone alone administered to a menopausal patient (see first paper of this series, p. 455, September issue of JOURNAL) and about twice as great as that of estrone when given with progesterone to this same individual in January, 1938.<sup>6</sup> These comparative recoveries are in keeping with the known comparative stabilities of these estrogens and with the protective action of progesterone against their destruction.

Some estrogen conversion prior to the last injections is indicated by the partition of the urinary estrogen metabolites. This partition is similar to that found during the follicular phase of a normal cycle (see Chart 1 of the third paper of this series), whereas the specimen was collected on the twentieth to twenty-second day. A biopsy at the end of this collection period and before the first injection revealed a proliferative endometrium. The urinary findings during and after injections in this experiment approach those of the luteal and premenstrual phase of the normal cycle<sup>6</sup> and Chart 1 of the third paper of this series and provide good evidence that an hormonal and endometrial situation similar to the normal was being artificially produced. The changes observed after injections were stopped are illustrative of the effect of estrogen and progesterone withdrawal upon estrogen metabolism. The increased rate of estrogen degradation just before and at the start of flow is the same as that observed at the onset of normal postovulatory menstruation.<sup>6</sup> and Chart 1 of the third paper of this series

Thus, according to the data, we were reproducing at regular intervals in this patient a normal situation which would not otherwise have pertained. We are inclined to the opinion that the *rapid* shift in estrogen metabolism which has been found consistently in our studies to follow estrogen and progestin withdrawal is concerned not only with the onset of flow but with the pituitary stimulation necessary for starting the ovary on a new cycle. By artificially supplying this stimulation seven consecutive times at intervals which approximated those of the normal cycle, we believe that the pituitary-ovarian discord from which this patient had been suffering since puberty twelve years ago was finally

An endometrial biopsy on October 18, before this last series of injections and on the twenty-second day of the cycle, showed normal proliferation with no evidence of secretory change. Therapy was discontinued. On November 28, the thirty-fourth day since the last catamenia, the patient spontaneously bled for one day only. Thirty-one days later a spontaneous normal five-day period occurred, a biopsy taken at the start of flow revealing secretory endometrium with predecidual change. On Jan. 11, 1942, the fourteenth day of the cycle, a slight stain was noted. On January 30, the thirty-third day since the December period, a normal five-day catamenia occurred. A biopsy at the start of flow again revealed secretory glands and predecidual changes. The patient is still (seven months since the last series of estrogen and progestin injections) having normal catamenia at thirty to thirty-three-day intervals with no intermenstrual bleeding.

Beginning in June, 1941, after two artificially-produced withdrawal catamenia, forty-eight-hour specimens of urine were studied, covering the twentieth to twenty-second day of each cycle (Chart 3). These specimens were all collected before any hormones were given and at least twenty-three days from the last series of injections. The findings, therefore, must reflect spontaneous ovarian activity.

In the June and July specimens the absence of any demonstrable estrone, the high percentage of activity in the estradiol fractions, the high  $T_{2n}$  to  $T_0$  ratios, and the large amounts of "unaccounted for"  $T_{2n}$  activity all reflect the rapid degradation and failure in conversion of secreted estrogens indicative of progestin deficiency. Including four specimens of the 1938 study,<sup>6</sup> these make a total of eleven urinalyses on this patient, when no hormones were being administered, in which the same partition of estrogen metabolites has pertained, seven having been collected during flow and four when the patient was not bleeding. This consistency makes the change in urinary findings in August and the following months of unquestionable significance.

Beginning in August, after the fourth artificially-produced menstruation, goodly amounts of estrone became demonstrable in the urine, the percentage of activity in the estradiol fractions decreased, the  $T_{2n}$  to  $T_0$  ratios became lower, and there was a progressive decrease, with each cycle, in the amount of "unaccounted for"  $T_{2n}$  activity. Although a biopsy on the twenty-second day of the October cycle showed only proliferative endometrium and although the first spontaneous period (in November) was extremely scant, we feel justified in assuming, on the basis of the urinary findings, that spontaneous cyclic ovarian secretion of progestin was occurring from August on, even though ovulation may not have occurred. Hisaw<sup>15</sup> has recently stated our own conviction that absence of ovulation or of an endometrium which may be considered histologically as secretory does not necessarily mean complete absence of luteal function. In fact, the preovulatory partition of estrogen metabolites in the normal cycle<sup>6, 11</sup>, and the third paper of this series suggests that some luteal secretion may precede rupture of the ovarian follicle.

No urine was collected in December preceding the second spontaneous flow which we know, from the biopsy, was postovulatory. A forty-eight-hour specimen in January on the twentieth to twenty-second day of the cycle, five days after "ovulation" staining and twelve days before another spontaneous catamenia from a secretory endometrium, showed amounts and partition of estrogen metabolites which point to the most

# GLOMERULAR FILTRATION AND RENAL BLOOD FLOW IN THE HYPERTENSIVE WOMAN AND IN POSTTOXEMIC HYPERTENSION

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IT HAS been repeatedly shown that hypertensive disease is characteristically accompanied by a reduction of renal blood flow<sup>1-3</sup> and a relative increase in glomerular filtration.<sup>3, 4</sup>

Chesley<sup>5</sup> has studied a number of women with hypertension following toxemias of pregnancy and has determined the renal blood flow by the diodrast clearance and the glomerular filtration by the urea clearance. A comparison of the values obtained for the posttoxemic hypertensive patient with those for hypertensive women who had never had toxemic pregnancies showed a moderate reduction in filtration in the former. These findings led him to believe that hypertension in the posttoxemic woman differed in etiology from that in the male or nonparous female with essential hypertension.

In Chesley's series the renal blood flow was determined by the diodrast clearance and the glomerular filtration by:  $\text{Urea clearance} / 0.60 = \text{Glomerular filtration}$ . This relationship is shown to be true in the average normal kidney in both dog and man<sup>6, 7</sup> but in the presence of renal damage the ratio of urea clearance to inulin clearance varied from 0.33 to 0.88.<sup>8, 9</sup> Chassis and Smith<sup>7</sup> sum up the use of the urea clearance in renal disease by stating that "as kidney damage decreases the ability of the kidney to resorb water, the urea clearance approaches the inulin clearance." If the hypertensive kidney is not normal, it would seem reasonable to suppose that the use of the urea clearance for the determination of glomerular filtration might lead to considerable error.

The high incidence of residual hypertension in patients having had toxemic pregnancies and the inability to demonstrate an increased incidence of hypertension in parous women when compared to nonparous women in any age group,<sup>10</sup> make it seem likely that the diseases in the male, female, and posttoxemic hypertensive are related. It has been demonstrated that renal blood flow is reduced post partum in the toxemias of pregnancy, while the glomerular filtration rises,<sup>11, 12</sup> thereby giving a picture similar to hypertensive disease. We<sup>13</sup> have been able to show normal filtration rates for posttoxemic patients with normal blood pressure readings.

interrupted. That the clinical success of this experiment was post hoc is indicated by the complete clinical history of the case as well as the urinary findings.

#### SUMMARY AND CONCLUSIONS

A patient whose menstrual history since puberty has duplicated every pattern of functional flowing has been studied and treated for eight years. The results herein reported cover the past sixteen months, during which large amounts of progesterone have twice been given to control profuse flow, estriol has been ingested over a three-month period in the hope of inhibiting ovarian activity, and seven series of progesterone and estradiol benzoate injections have been given cyclically, these finally accomplishing the desired objective, namely, the establishment of spontaneous and regular ovulatory cycles.

Urinalyses for estrogen metabolites throughout this investigation have confirmed previously reported conclusions concerning estrogen and progestin metabolism in women and have led to the following general conclusions: (1) Functional flowing is associated with a progestin deficient metabolism of estrogen and results from fluctuations in ovarian secretion in the absence of adequate luteal control; (2) progesterone, in large amounts, constitutes a specific therapeutic agent for the production of a more normal estrogen metabolism and the control of functional bleeding; (3) estriol, although well absorbed from the intestinal tract and less rapidly destroyed than estradiol or estrone, is comparatively ineffective, possibly because of its relative stability, in influencing pituitary-ovarian activity; (4) estrogen and progesterone withdrawal results not only in normal endometrial bleeding but in a sudden increase in the rate of estrogen destruction which may provide a necessary stimulus for the normal growth and maturation of ovarian follicles; (5) if this stimulus is artificially supplied at monthly intervals, a normal pituitary-ovarian cycle may be established which will continue after cessation of cyclic therapy.

*(The third and fourth sections of this presentation will follow in an early issue.)*



any one clearance. We have not discarded these values in any instance in which they check within 10 per cent of the mean of the clearances run on that patient.

## RESULTS

*Hypertension Occurring in Nonparous Patients.*—(Table I.) The inulin clearances in this group of patients averaged 82 c.c. per minute, with a range of 54 to 150 c.c. per minute. The diodrast clearances averaged 409 c.c. per minute and the renal blood flow was calculated at 675 c.c. per minute. The filtration fraction was 21.6 as determined by the inulin clearance but when calculated from the urea clearance/0.60, it was found to be 23.6. The average urea clearance was 58.0 c.c. per minute and the uric acid clearance averaged 23 c.c. per minute.

*Posttoxemic Hypertensive Women.*—(Table II.) The inulin clearance in this group was found to average 93 c.c. per minute. The diodrast clearances averaged 434 c.c. per minute and this gave a calculated renal blood flow of 720 c.c. per minute. The filtration fraction as determined from the inulin clearance was 21.7 but determined from the urea clearance/0.60, was found to be 29.0. The average urea clearance was 75 c.c. per minute, and the uric acid clearance averaged 30.7 c.c. per minute.

## DISCUSSION

All of our "posttoxemic" women are classified by this broader term rather than into the subgroups of mild pre-eclampsia, severe pre-eclampsia, hypertensive disease, or renal disease, because we were unable to obtain previous renal function tests, eye ground examinations or satisfactory follow-up examinations of blood pressure and urine. We realize that each of these syndromes may in itself be an entirely separate clinical and pathologic entity.

The average age of the posttoxemic women is moderately lower than that of the nonparous group. The nonparous group, as is to be expected, seems to have more evidence of vascular and renal changes when one compares the blood pressure levels (185/110 in the nulliparous group as compared to 157/100 in the parous) and urea clearances in the two groups (58 c.c. per minute for the nulliparous and 75 c.c. per minute for the parous group). In spite of this apparent difference in vascular and renal status, there is no real difference in the glomerular filtration, renal blood flow, or filtration fraction.

Our glomerular filtration values as determined by inulin clearance are noticeably lower than those of normals (116 c.c. per minute) and also than those of Chesley<sup>5</sup> (106 c.c. per minute, urea/0.60) and Friedman<sup>3</sup> (104 c.c. per minute, clearances on 4 women). The diodrast and renal blood flow values (675 to 720 c.c. per minute renal flow) in general compare favorably with those of the above workers in both male and female hypertensives and seem to be merely proportional to the level of the blood pressure and to the length of time hypertensive and post partum. When the glomerular filtration is determined by urea clearance/0.60, we find that the parous women have a high filtration

## MATERIALS AND METHODS

Our series included 23 patients who were divided into two groups. The nonparous hypertensive group consisted of 10 patients who had blood pressure levels of 150-240/90-170, the average level being 185/110. The posttoxemic group consisted of 13 women who were known to have had pregnancies complicated by hypertension and albuminuria and whose records during these pregnancies are available since all had been delivered in the old or new lying-in Hospital of New York. The blood pressure readings varied from 130-230/90-130, averaging 157/100.

All patients were thoroughly studied clinically and examination of eye grounds, heart, and vascular status made. They varied in age from 23 to 61 years, and the toxemic patients had been pregnant from 1 to 39 years previously.

All clearances were run by two individuals and the method was standard. One thousand cubic centimeters of water were given by mouth the night preceding the test and 200 c.c. more were given at 5:00 A.M. and 6:00 A.M. At 6:00 A.M. the bladder was catheterized with a No. 14 soft rubber catheter and an intravenous drip started at 4 c.c. per minute, containing 15 c.c. of 10 per cent inulin and 10 c.c. of diodrast in 500 c.c. of 5 per cent glucose. A priming dose of 10 c.c. of 10 per cent inulin and 1 c.c. of diodrast was given at the beginning of the infusion. After twenty to thirty minutes the urinary bladder was emptied by washing two or three times with 20 to 30 c.c. of distilled water, and this was evacuated by inflating the bladder once with 50 to 100 c.c. of air. Clearance periods varied from ten to thirty minutes and an attempt was made to secure 80 to 120 c.c. of urine during each period. Three consecutive clearance periods were run on each patient. Blood values were determined in the midpoint of each the first and third clearance periods and the value of the second calculated by interpolation.

All determinations of blood levels were done on plasma except for blood urea which was made on whole blood. The inulin values on plasma and urine were done following incubation with 20 per cent yeast solution and precipitation with Somogyi's technique, by the method of Alving, Rubin, and Miller.<sup>14</sup> Diodrast was determined after precipitation of the plasma by 10 per cent trichloroacetic acid by the method of Alpert,<sup>15</sup> and this method was used on the urine in dilution of 1:250. Urea was determined on both the blood and the urine in 1:10 dilution by Van Slyke's manometric method<sup>16</sup> and uric acid in plasma and urine by the Folin technique.<sup>17</sup>

All clearances which failed to check within 10 per cent of the mean of the three clearances were discarded and all were recalculated on the basis of 1.73 square meters of surface area.

The filtration fraction was determined by  $\frac{\text{Inulin clearance}}{\text{Diodrast clearance}}$  and the renal blood flow by  $\frac{\text{Diodrast clearance}}{1 - \text{Hematocrit}}$ .

We have noted both in this series and in patients previously tested<sup>11, 13</sup> that on some occasions the urea clearance has shown higher values than the inulin clearance. This difference has generally been within the error of the method, which we feel is not less than 10 per cent on

TABLE II. CLINICAL DATA AND TABULATION OF CLEARANCE VALUES ON PATIENTS WITH HYPERTENSION. ALL PATIENTS HAD SUSTAINED A PREGNANCY COMPLICATED BY HYPERTENSION AND ALBUMINURIA

| PATIENT       | AGE | PARITY | BLOOD PRESSURE | YEAR OF TOXEMIC PREGNANCY | HEMATOCRIT | INULIN CLEARANCE C.C./MIN. | DIOBRAST CLEARANCE C.C./MIN. | RENAL BLOOD FLOW C.C./MIN. | UREA CLEARANCE C.C./MIN. | URIC ACID CLEARANCE C.C./MIN. | FILTRATION FRACTION | UREA 0.60 | UREA F.P. 0.60 |
|---------------|-----|--------|----------------|---------------------------|------------|----------------------------|------------------------------|----------------------------|--------------------------|-------------------------------|---------------------|-----------|----------------|
| 1B            | 61  | 5-3-2  | 230/120        | 1903, 1905                | 40         | 93 81 102                  | 560 530 618                  | 930 885 1030               | 61.0                     | 28.0 26.0 26.0                | 0.16 0.15 0.17      | 100.0     | 0.178          |
| 2B            | 55  | 2-0-2  | 160/110        | 1909, 1911                | 38         | 96 85                      | 82 492 465 435               | 792 750 700                | 68.8                     | 45.0 42.2 37.0                | 0.18 0.19 0.195     | 111.0     | 0.239          |
| 3B            | 43  | 4-2-2  | 180/110        | 1916, 1919                | 40         | 70 75                      | 73 390 475 375               | 650 780 625                | 61.9                     | 61.9                          | 0.18 0.16 0.19      | 106.7     | 0.217          |
| 4B            | 33  | 3-0-3  | 160/100        | 1931, 1938                | 40         | 95 85                      | 92 347 328 348               | 580 492 580                | 68.7                     | 36.7 32.2 28.5                | 0.28 0.26 0.26      | 107.3     | 0.314          |
| 5B            | 37  | 5-1-3  | 160/100        | 1939                      | 37         | 53 52                      | 71 405 372                   | 655 600                    | 56.0                     | 67.1                          | 0.13 0.19           | 112.0     | 0.289          |
| 6B            | 33  | 1-0-1  | 145/90         | 1940                      | 35         | 93 82                      | 470 465 438                  | 720 660                    | 79.2                     | 37.5 33.3                     | 0.21 0.19           | 128.0     | 0.282          |
| 7B            | 23  | 1-0-0  | 144/94         | 1941                      | 46         | 75 84                      | 388 365 210                  | 690 650 550                | 58.0                     | 22.0 18.0 17.5                | 0.19 0.23           | 100.0     | 0.282          |
| 8B            | 33  | 2-0-1  | 135/90         | 1941                      | 40         | 119 100                    | 290 330                      | 485 550                    |                          |                               | 0.41 0.30           |           |                |
| 9B            | 34  | 3-1-1  | 140/90         | 1941                      | 34         | 76 84                      | 472 450 460                  | 715 680                    | 61.0                     | 55.3                          | 0.16 0.19           | 185.0     | 0.346          |
| 10B           | 28  | 1-0-1  | 150/100        | 1941                      | 38         | 128 123                    | 119 580 530 495              | 935 854 798                | 119.8                    | 98.6                          | 0.22 0.23 0.24      | 168.3     | 0.497          |
| 11B           | 23  | 1-0-1  | 120/90         | 1941                      | 32         | 101 131                    | 344 333                      | 510 490                    | 91.6                     | 112.9                         | 0.29 0.39           | 133.3     | 0.308          |
| 12B           | 43  | 7-5-0  | 150/110        | 1941                      | 40         | 86 74                      | 73 430 428 380               | 716 714 670                | 77.1                     | 83.4                          | 0.20 0.17 0.19      | 183.3     | 0.299          |
| 13B           | 34  | 2-1-1  | 150/90         | 1941                      | 40         | 144 123 142                | 610 606 625                  | 1020 1020 1030             | 103.5                    | 106.9 122.2                   | 0.24 0.20 0.23      | 126.1     | 0.290          |
| Total average |     |        | 157/100        |                           |            | 93.0                       | 434.5                        | 720.8                      | 75.7                     | 30.7                          | 0.217               |           |                |

TABLE I. CLINICAL DATA AND TABULATION OF CLEARANCE VALUES ON PATIENTS WITH HYPERTENSION.  
NONE OF THESE PATIENTS HAD BEEN GRAVID

| PATIENT       | AGE | PARITY | BLOOD PRESSURE | ALBUMIN | HEMATOCRIT | INULIN CLEARANCE C.C./MIN. | DIODRAST CLEARANCE C.C./MIN. | RENAL BLOOD FLOW C.C./MIN. | UREA CLEARANCE C.C./MIN. | URIC ACID CLEARANCE C.C./MIN. | FILTRATION FRACTION | UREA 0.60 | UREA 0.60 F.F. |
|---------------|-----|--------|----------------|---------|------------|----------------------------|------------------------------|----------------------------|--------------------------|-------------------------------|---------------------|-----------|----------------|
| 1A            | 40  | 0-0-0  | 150/90         | Neg.    | 40         | 110                        | 670                          | 1033                       | 42.9                     | 10.2                          | 0.18                | 68.8      | 0.102          |
| 2A            | 43  | 0-0-0  | 160/100        | Neg.    | 32         | 97                         | 400                          | 680                        | 89.0                     | 9.8                           | 0.22                | 148.0     | 0.351          |
| 3A            | 44  | 0-0-0  | 240/170        | +       | 40         | 54                         | 150                          | 250                        | 23.7                     | 15.9                          | 0.36                | 48.7      | 0.336          |
| 4A            | 44  | 0-0-0  | 180/100        | Neg.    | 41         | 80                         | 556                          | 942                        | 61.3                     | 37.8                          | 0.17                | 94.3      | 0.188          |
| 5A            | 37  | 0-0-0  | 170/100        | Neg.    | 35         | 57                         | 428                          | 653                        | 73.7                     | 30.8                          | 0.13                | 123.0     | 0.309          |
| 6A            | 62  | 0-0-0  | 240/130        | Neg.    | 41         | 100                        | 440                          | 750                        | 59.8                     | 29.7                          | 0.23                | 97.9      | 0.221          |
| 7A            | 51  | 0-0-0  | 170/95         | Neg.    | 45         | 108                        | 560                          | 1010                       | 63.7                     | 28.9                          | 0.19                | 118.0     | 0.218          |
| 8A            | 37  | 0-0-0  | 230/130        | Neg.    | 37         | 87                         | 365                          | 580                        |                          |                               | 0.24                | 0.23      |                |
| 9A            | 48  | 0-0-0  | 150/95         | Neg.    | 41         | 60                         | 445                          | 745                        | 58.2                     | 19.4                          | 0.17                | 100.0     | 0.239          |
| 10A           | 50  | 0-0-0  | 160/100        | Neg.    | 40         | 64                         | 327                          | 550                        | 71.1                     | 30.9                          | 0.20                | 96.7      | 0.236          |
| Total average |     |        | 185/110        |         | 39         | 82.8                       | 409.1                        | 675.8                      | 58.0                     | 23.0                          | 0.216               |           |                |

the renal blood vessels are initiated by the hypertension, and that the causative agent of the elevated pressure (reduction of renal pulse pressure?) is the primary factor in this disease.

### CONCLUSIONS

No evidence is found to support the theory that posttoxemic hypertension varies from hypertension in the nulliparous female.

Substitution of inulin for urea clearances in the determination of glomerular filtration shows no significant difference in glomerular filtration in the posttoxemic women when compared to those who have had no pregnancies.

Our data show that afferent arteriolar constriction plays a pronounced part in the regulation of renal blood flow in hypertension and suggests that the functional status of this arteriole may well explain most of the alteration of renal function found in this disease.

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fraction while that of the nulliparous women parallels the inulin clearance closely. We are unable to explain this difference, but it seems likely that it is due to decreased resorption of urea.

In the toxemias of pregnancy and in the posttoxemic hypertensives, several workers<sup>12, 18</sup> have postulated the existence of efferent arteriolar constriction added to a thickening of the glomerular membrane to permit a reduced glomerular filtration and control of the renal blood flow.

Smith<sup>1</sup> postulated the efferent arteriolar control of renal blood flow not because of the apparent increase in glomerular filtration, but because of the anatomic evidence of afferent arteriolar thickening in arteriolar disease<sup>19</sup> and the lack of demonstrable hypertension in the peripheral capillary bed of hypertensive patients,<sup>20</sup> it would seem likely that most of the control of renal flow and glomerular filtration is effected in the afferent arteriole.

Smith<sup>21</sup> has recently presented evidence that the reduced glomerular filtration rate in "toxemias of pregnancy" is found by using mannose as well as inulin and states that the difference in molecular size would argue against the thickening of the glomerular membrane as the etiologic factor. Lamport<sup>22</sup> has recently attempted to apply Poiseuille's law to the arterioles of the kidney and has been able to arrive at definite values for resistance in the afferent and efferent arterioles. We have applied his formula to our findings and have found that although significant increases can be found in the resistance of the efferent arteriole in hypertension (Table III), they are dwarfed by the changes in afferent resistance by even minimal increases in mean systemic blood pressure.

TABLE III. CALCULATED RESISTANCE IN THE AFFERENT AND EFFERENT ARTERIOLES IN THE POSTTOXEMIC HYPERTENSIVE AND THE NULLIPAROUS HYPERTENSIVE

|                                  | MEAN<br>BLOOD<br>PRES-<br>SURE | INULIN<br>CLEAR-<br>ANCE<br>G.C./MIN. | DIO-<br>DRAST<br>CLEAR-<br>ANCE<br>G.C./MIN. | RENAL<br>BLOOD<br>FLOW<br>C.C./MIN. | RESIST-<br>ANCE<br>OF AF-<br>FERENT<br>ARTE-<br>RIOLES<br>(R. A.)* | RESIST-<br>ANCE<br>OF EF-<br>FERENT<br>ARTE-<br>RIOLES<br>(R. E.)* | TOTAL<br>RESIST-<br>ANCE<br>(R.) | R.A./R.E.* |
|----------------------------------|--------------------------------|---------------------------------------|--|-------------------------------------|--|--|----------------------------------|------------|
| Hyperten-<br>sion                | 147                            | 82.8                                  | 404.1  | 675.8                               | 99.1   | 32.1   | 131.2                            | 2.08       |
| Posttoxemic<br>hyperten-<br>sion | 123                            | 93.0                                  | 434.5  | 720.8                               | 67.3   | 30.1   | 97.4                             | 2.23       |
| Normal                           | 100                            | 120.0                                 | 600.0  | 1020.0                              | 19.5   | 14.4   | 33.9                             | 1.35       |

$$*R. E. = \frac{(1 - 0.47F)(Po' - 16.4)}{HD}$$

$$R. A. = \frac{Pm - Po' - 40}{HD}$$

HD, Renal blood flow

Po', Osmotic pressure of plasma

Pm, Mean systemic blood pressure

F, Filtration fraction:  $\frac{\text{Inulin clearance}}{\text{Diodrast clearance}}$

These results and previous findings in nonhypertensive posttoxemic patients would tend to produce evidence that the changes in caliber of

TABLE I. THE INCIDENCE OF POSTERIOR ROTATION OF THE OCCIPUT  
(SINGLE-FETUS, TERM PREGNANCIES)

|                                      |       |       |
|--------------------------------------|-------|-------|
| Total vaginal deliveries             | 4,164 |       |
| Primary occipitoposterior positions* | 1,041 | 25.0% |
| Posterior rotations of the occiput   | 96    | 2.3%  |

\*The estimate of the number of primary occipitoposterior positions occurring in our patients was based on the assumption that the normal distribution, as calculated from the combined data of Danforth,<sup>5</sup> Caldwell, Moloy, and D'Esopo,<sup>6</sup> and Calkins,<sup>7</sup> was applicable to our clinical material.

*Fetal Size.*—The relation of infant size to posterior rotation of the occiput was analyzed first by investigation of the mean birth weight of term infants. It may be noted (Table II) that the infants of the women of the special study group were 110 Gm. heavier on the average than the babies of all clinic patients delivered during the same period. One patient delivered spontaneously, face-to-pubis, an infant weighing 4,730 Gm.

The second method of analysis was based upon the frequency of posterior rotation of the occiput in premature labors. In the 310 patients who delivered viable infants under 2,500 Gm., the incidence was 2.3 per cent. This frequency was identical with that noted in term deliveries (Table III).

*Parity.*—The parity of women who exhibited posterior rotation of the occiput was compared with the parity of all clinic patients delivered during the period of study. The incidence of nulliparity in the special study group was not significantly lower than the clinic average (Table IV). No correlation could be established between parity and fetal birth weight.

TABLE II. THE RELATION OF FETAL SIZE TO POSTERIOR ROTATION OF THE OCCIPUT

| TERM, VAGINAL DELIVERIES               | AVERAGE BIRTH WEIGHT OF INFANTS IN GRAMS |
|--|--|
| All patients (4,164)                   | 3,310                                    |
| Patients with posterior rotations (96) | 3,420                                    |

TABLE III. THE RELATION OF FETAL MATURITY TO POSTERIOR ROTATION OF THE OCCIPUT

| MATURITY OF THE FETUS AT DELIVERY | FREQUENCY OF POSTERIOR ROTATION PER CENT |
|-----------------------------------|--|
| Term (4,164)                      | 2.3                                      |
| Premature (310)                   | 2.3                                      |

TABLE IV. THE RELATION OF PARITY TO POSTERIOR ROTATION OF THE OCCIPUT

| TERM, VAGINAL DELIVERIES               | FREQUENCY OF NULLIPARITY PER CENT |
|--|-----------------------------------|
| All patients (4,164)                   | 27.5                              |
| Patients with posterior rotations (96) | 25.3                              |

*Size of Maternal Pelvis.*—The mean pelvic dimensions of the special study group were obtained from roentgenographic films and arranged according to pelvic plane. Since no measurements of a control group were available from our clinic, it was assumed that the data collected

## POSTERIOR ROTATION OF THE OCCIPUT DURING LABOR

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ON THE maternity service of the Hospital of the University of Pennsylvania, 96 parturient women were observed in whom posterior rotation of the occiput occurred during the course of labor. In about three-fourths of these patients, the infant was born spontaneously, face-to-pubis. Since this outcome was not expected, we decided to study these women as a special group. We wanted to evaluate some of the factors reputed to bring about posterior rotation of the occiput, and to determine whether any special risk was associated with this variation in the labor mechanism.

### MATERIAL AND METHODS

The patients were selected from the Ward Service during the five-year period from 1936 to 1940, inclusive. Special study was limited to those women who exhibited vulvar crowning of the fetal head with the face-to-pubis. To simplify the analysis further, deliveries of twins, and those of infants under 2,500 Gm. were studied separately.

The bony pelvis of the women selected were examined roentgenographically. Pelvic variations were described after the manner of Caldwell, Moloy, and D'Esopo.<sup>1</sup> Mensuration of pelvic dimensions was carried out according to the method of Ball.<sup>2</sup> In addition to the data obtained from the roentgenograms, the clinical records of these patients were compared with those of control clinic groups. No new mode of comparison was attempted. Instead, the investigation was centered on factors commonly mentioned in current textbook discussions of this subject.<sup>3, 4</sup>

### RESULTS

*Frequency.*—During the period covered by the study, 4,164 women were delivered vaginally of single-fetus, term pregnancies. Posterior rotation of the occiput was exhibited by 96 of these patients, an incidence of 2.3 per cent (Table I). The occiput rotated posteriorly from a primary posterior position in 87 patients, and from an occipitotransverse position in 9 women. No instance of posterior rotation was observed to follow occipitoanterior engagement of the fetal head.

Unfortunately, the true incidence of occipitoposterior position at the time of engagement could not be reported from our material, because many of the patients were far advanced in labor when admitted to the hospital. However, if the combined data of Danforth,<sup>5</sup> Caldwell, Moloy, and D'Esopo,<sup>6</sup> and Calkins<sup>7</sup> can be applied to our patients, about 1,041, or 25 per cent, had occipitoposterior positions of engagement. Only 87 of these women were known to exhibit posterior rotation, or about 1 out of every 12 patients.



forepelvis presented the only examples of pelvic deformity. No significant correlation could be established between the occurrence of posterior rotation of the occiput and the shape of the sacrum, number of sacral segments, or inclination of the plane of the pelvic inlet.

In order to test the frequency of posterior rotation in the various types of maternal pelvis, we have utilized the combined data of Caldwell, Moloy,<sup>9</sup> and D'Esopo,<sup>9</sup> Rappaport and Scadron,<sup>11</sup> and Steele, Wing and McLane<sup>12</sup> to estimate the total number of pelvises of each type that might be expected to have occurred in our total 4,164 patients. Then, we have listed the known frequency with which each type of normal pelvis was observed in the 94 patients showing posterior rotation of the occiput (Table VII). Note that even in the anthropoid group, the frequency of posterior rotation was only 6.5 per cent. This low incidence can be accounted for, in part, by the reasonable assumption that about two-thirds of the 1,041 patients with anthropoid pelvises presented anterior or transverse positions of engagement of the fetal head. However, primary occipitoposterior positions probably occurred in one-third of this group,<sup>6</sup> or in about 345 women. Of these, only 68 patients, or 1 out of every 5, really exhibited posterior rotation.

TABLE VII. THE FREQUENCY OF POSTERIOR ROTATION OF THE OCCIPUT IN VARIOUS TYPES OF MATERNAL PELVES

| PELVES      |  | THE OBSERVED FREQUENCY OF POSTERIOR ROTATION |          |
|-------------|--|--|----------|
| TYPE        | ESTIMATED NUMBER AMONG 4,164 PATIENTS* | NUMBER PATIENTS                              | PER CENT |
| Anthropoid  | 1,041                                  | 68   | 6.5      |
| Gynecoid    | 1,999                                  | 17   | 0.9      |
| Platyelloid | 291                                    | 5  | 1.7      |
| Android     | 833                                    | 4  | 0.5      |

\*The estimate of the distribution of each type of pelvis among our 4,164 parturient women was based upon the assumption that the normal distribution, as calculated from the combined data of Caldwell, Moloy, and D'Esopo,<sup>9</sup> Rappaport and Scadron,<sup>11</sup> and Steele, Wing, and McLane,<sup>12</sup> was applicable to our clinical material.

*Repetition of Posterior Rotation.*—The 72 multiparous women of the study group have given birth to 306 infants. Since nearly half of these babies were born in other hospitals, or in the homes of the patients, the position of the occiput at the time of delivery could not be determined in a significant number. However, 13 of the 72 multiparas were known to have exhibited posterior rotation of the occiput in two or more labors. It may be noted that 11 of these 13 women have exhibited anterior rotation in another labor. Separate analysis made of the roentgenograms and clinical records of these 13 women did not reveal any significant variation in fetal size, pelvic size, nor pelvic shape.

*Delivery.*—The mode of delivery of the 96 patients with posterior rotation of the occiput was shown in Table VIII. Note that 78 women delivered spontaneously, face-to-pubis, whereas 17 patients required the assistance of outlet forceps. In only 1 patient was the Scanzoni maneuver utilized. In spite of the low operative incidence, labor was not unduly prolonged (Table IX).

*Maternal and Infantile Morbidity.*—The morbidity observed among the patients and their infants in the study group was compared with

by Thoms<sup>8</sup> from 200 normal women could be used for comparison. As can be seen in Table V, there was surprising similarity in the dimensions of each level of the birth canal. No evidence existed of pelvic contraction at the inlet, midpelvic, or outlet planes. The difference in length of the mean true conjugate diameters probably would not be significant statistically. However, the greater depth of the posterior segment of the inlet of women who exhibited posterior rotation may be a true variation from the normal.

*Shape of Maternal Pelvis.*—The various bony pelvic configurations of our patients were noted in Table VI. For comparison, we have recorded the distribution of pelvic types in a control group of 215 normal patients studied by Caldwell, Moloy, and D'Esopo.<sup>9</sup> It will be seen that a considerably higher than normal proportion of anthropoid pelvises occurred among patients exhibiting posterior rotation of the occiput. As Thoms<sup>10</sup> has noted in women with posterior positions, the principal inlet configuration observed in the study group consisted of a deep fore-pelvis with a narrow angle, and a rounded posterior segment. We failed to find android posterior segments except in combination with deep anthropoid forepelves. The few android pelvises noted otherwise had a rounded posterior segment. Even the flat pelvises were large and displayed sufficient backward sacral displacement to feature the capacious posterior space at midplane and lower pelvic levels which was common to this group. Two patients with minor grades of asymmetry of the

TABLE V. THE RELATION OF MATERNAL PELVIC SIZE TO POSTERIOR ROTATION OF THE OCCIPUT

| AVERAGE<br>PELVIC DIMENSIONS* | POSTERIOR ROTATIONS<br>(96)<br>CM. | CONTROL GROUP†<br>(200)<br>CM. |
|-------------------------------|------------------------------------|--------------------------------|
| Inlet:                        |                                    |                                |
| Anteroposterior               | 11.9                               | 11.6                           |
| Posterior sagittal            | 4.9                                | 4.4                            |
| Transverse                    | 12.3                               | 12.3                           |
| Midplane:                     |                                    |                                |
| Anteroposterior               | 12.5                               | 12.3                           |
| Transverse                    | 10.3                               | 10.2                           |
| Outlet:                       |                                    |                                |
| Transverse                    | 9.1                                | 9.1                            |

\*All dimensions obtained from roentgenograms of the pelvis.

†Data of Thoms.<sup>8</sup>

TABLE VI. THE RELATION OF MATERNAL PELVIC SHAPE TO POSTERIOR ROTATION OF THE OCCIPUT

| TYPE OF PELVIS* | POSTERIOR ROTATIONS<br>(96)<br>PER CENT | CONTROL GROUP†<br>(215)<br>PER CENT |
|-----------------|---|-------------------------------------|
| Anthropoid      | 70.8                                    | 26.4                                |
| Gynecoid        | 17.7                                    | 39.5                                |
| Platypelloid    | 5.2                                     | 6.3                                 |
| Android         | 4.2                                     | 27.8                                |
| Asymmetrical    | 2.1                                     | ----                                |

\*Pelvises of mixed type were classified according to their predominant features, i.e. anthropogynecoid, and androanthropoid pelvises were collected in the anthropoid group, androgynecoid pelvises in the android group, and all flat types in the platypelloid division. The gynecoid group included pelvises with only minor variants from the pure form.

†Data of Caldwell, Moloy, and D'Esopo.<sup>9</sup>

It has been taught that a badly relaxed, or torn muscular pelvic floor of the mother may be responsible for failure of anterior rotation of the occiput.<sup>3</sup> This idea, which probably originated with Dubois,<sup>15</sup> lacks confirmatory data. Dawson<sup>14</sup> was unable to correlate posterior rotation of the occiput with multiparity. Our observations agree with his, and make it seem unlikely that the muscular pelvic floor plays a significant role in this mechanism.

Attention has been directed to the relation between the bony pelvis and the occipitoposterior position. Certain authors<sup>16, 17</sup> have referred to the importance of pelvic contraction in the etiology of this variation in the labor mechanism. On the other hand, Fabre and Trillat,<sup>18</sup> Thoms,<sup>10</sup> and Hastings and Young<sup>19</sup> have reported that the anteroposterior dimensions of the pelves of these patients were increased. In the present study, wherein the problem of disproportion was eliminated by the method of selection of patients, the dimensions of the pelves were within the limits of normal variation. As Thoms,<sup>10</sup> and Caldwell, Moloy, and D'Esopo<sup>20</sup> have noted previously, the anthropoid inlet configuration with ample posterior space at lower pelvic planes was observed. We were unable to confirm the report of Hanson<sup>21</sup> that transverse midpelvic contraction was a significant variation in patients with persistent occipitoposterior positions.

The frequency of the anthropoid pelvic shape in parturient women exhibiting posterior rotation of the occiput should not lead to the conclusion that a high incidence of face-to-pubis delivery may be expected in anthropoid pelves in general. In addition to this shape of pelvic inlet, ample anteroposterior space must be available at lower pelvic levels and the fetal head should have begun descent into the pelvis with the occiput posterior. Even when this combination of factors is operating, the probability of face-to-pubis delivery is only about 1:5. It would appear, therefore, that there has been a failure to work out other factors predisposing to posterior rotation. Study of deflexion attitudes of the head, shape of the fetal head, position of the placenta, and axis of the cervix may give additional information.

The classification of posterior rotation of the occiput as an anomaly of the mechanism of labor seems to be based mainly on the infrequency of its occurrence. The clinical results obtained in our patients, and in those of Dawson,<sup>14</sup> raise doubt of pathologic significance. Additional maternal effort was required for spontaneous delivery, and the perineal stage did not progress with quite the same ease observed in anterior positions of the occiput. However, no harm to mother or child attended the outcome when complete posterior rotation of the occiput was exhibited. We hasten to add that these remarks should not be construed to refer to midpelvic "arrests" with the occiput posterior. Incomplete rotation of the occiput in a posterior, or any other position, introduces factors beyond the scope of this presentation.

TABLE VIII. THE MODE OF DELIVERY OF 96 PATIENTS WITH POSTERIOR ROTATION OF THE OCCIPUT

| DELIVERY                    | PATIENTS |
|-----------------------------|----------|
| Face-to-pubis:              |          |
| Spontaneous                 | 78       |
| Low forceps extraction      | 17       |
| After rotation of the head: |          |
| With forceps                | 1        |

TABLE IX. THE AVERAGE DURATION OF LABOR IN PATIENTS WITH POSTERIOR ROTATION OF THE OCCIPUT

| TYPE OF DELIVERY            | NULLIPARA         |                    | MULTIPARA         |                    |
|-----------------------------|-------------------|--------------------|-------------------|--------------------|
|                             | FIRST STAGE HOURS | SECOND STAGE HOURS | FIRST STAGE HOURS | SECOND STAGE HOURS |
| Spontaneous deliveries (78) | 16.5              | 2.3                | 7.9               | 0.8                |
| All deliveries (96)         | 18.5              | 2.8                | 8.1               | 1.0                |

TABLE X. THE MORBIDITY OF DELIVERY IN PATIENTS EXHIBITING POSTERIOR ROTATION OF THE OCCIPUT

| MORBIDITY                 | POSTERIOR ROTATIONS (96)<br>PER CENT | CONTROL GROUP* (4,164)<br>PER CENT |
|---------------------------|--------------------------------------|------------------------------------|
| Maternal mortality rate   | 0.0                                  | 0.1                                |
| Infant mortality rate     | 0.0                                  | 2.7                                |
| Operative delivery rate   | 18.8                                 | 8.5                                |
| Lacerations and injuries: |                                      |                                    |
| Second-degree tears       | 13.5                                 | 10.0                               |
| Third-degree tears        | 2.0                                  | 0.5                                |
| Febrile morbidity rate    | 12.5                                 | 11.6                               |

\*All women delivered vaginally of term infants in the University Hospital during the period of the study.

that of all patients of the clinic who were delivered of term infants during the same period. It will be noted in Table X, that the only significant morbidity ascribable to the condition, or to the accompanying operative maneuvers was a slightly increased incidence of injury to the perineum.

#### DISCUSSION

Current textbooks of obstetrics<sup>3, 4</sup> list causes of posterior rotation of the occiput which often seem to lack foundation in fact. Thus, emphasis has been placed on the importance of the fetal head being too small to engage those forces of labor presumed to bring about anterior rotation.<sup>3</sup> However, aside from the observations by Plass<sup>13</sup> on a small number of premature infants, very little factual data have been offered to substantiate this point of view. Dawson,<sup>14</sup> on the contrary, has noted that the average birth weight of infants delivered face-to-pubis was about the same as that of babies born with the occiput anterior. Our data lend support to Dawson's observation, and indicate that fetal size can hardly be a significant factor in posterior rotation of the occiput.

## SPONTANEOUS ABORTION AND ITS TREATMENT WITH PROGESTERONE

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THE age-old controversy as to whether heredity or environment plays the greater role in human development is not confined to the post-partum period of life, but involves intrauterine life as well, and the gametes, themselves, in a consideration of the cause of spontaneous abortion. Particularly is this true in those cases without obvious cause. Upon careful study, causes are sometimes found which are not obvious, such as hypothyroidism, for example.

The work of many able observers has established beyond any doubt that many of these early abortuses are pathologic, from 50 to 80 per cent, according to different workers. Mall<sup>1</sup> has divided pathologic ova into seven groups, from those showing villi only to a chorion and amnion containing a macerated embryo. Normal embryos were those in which the embryos were normal or possessing only localized anomalies. Hertig and Edmonds<sup>2</sup> found pathologic ova in 47.4 per cent of 53 consecutive cases of spontaneous abortion, and in these hydatidiform degeneration was found in 66 per cent. The mean duration of the pregnancy in these cases was ten and two-tenths weeks, which is in agreement with clinical experience that most spontaneous abortions occur between the second and third months.

The difference of opinion begins when an attempt is made to account for the pathologic abortuses. These opinions fall into two divisions: (1) that abnormalities in the germ cells themselves are responsible for the pathologic ova or embryos, and (2) that the observed pathologic abortuses are due to abnormalities in the maternal developmental environment.

Mall,<sup>1</sup> after an exhaustive study of abortuses, expressed it as his belief that all of these abnormalities, from the least to the greatest, were due to faulty implantation. He says, "In my paper on monsters, I stated that on account of faulty implantation of the chorion, the nutrition of the embryo is affected so that if the ovum is very young the entire embryo is soon destroyed, leaving only the umbilical vessels within the chorion, and this also soon disintegrates, leaving only the chorionic membrane, which in turn collapses, breaks down and finally disappears entirely. . . . I have attempted to point out that the primary cause is in the environment of the egg, and that the arrested development is associated with destruction of tissue."

Meyer<sup>3</sup> on the other hand does not agree. He says, "Although we know very little about the existence of abnormal ova, the relative fre-

## SUMMARY

1. Posterior rotation of the occiput was observed in 96 of the 4,164 patients who were delivered vaginally of term infants.

2. Posterior rotation of the occiput was exhibited by one patient out of every twelve who presented occipitoposterior engagement of the fetal head. It was not noted after primary occipitoanterior positions, and only rarely after transverse engagement.

3. No etiologic significance could be attributed to small fetal size, relaxation of maternal soft tissues, nor gross pelvic deformity.

4. The mean dimensions of the bony pelvis of patients of the study group were only slightly different from those of a control group of women. A trend was noted toward anteroposterior spaciousness at all pelvic levels.

5. A high incidence of anthropoid pelvis was observed in the par-turient women studied. Android pelvic types were seen rarely.

6. Posterior engagement of the occiput in an anthropoid pelvis introduced a probability of complete posterior rotation in one out of five patients.

7. No special pathologic significance could be attached to this variation in the labor mechanism.

I wish to express my appreciation to Dr. Carl Bachman for guidance in this study.

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the human animal has not proved to be unique in any fundamental biologic particular from the rest of the animal kingdom, there is at present no basis for a belief that his germ cells are the one exception.

These two trends of opinion have a distinct bearing upon us as clinicians, when faced with the problem of abortion in the human being. Granting that from 50 to 80 per cent of all abortuses are pathologic, if we are convinced that these result primarily from defects in the germ cells themselves, then it is obvious that no treatment directed toward the mother, of any nature whatever, whether begun as soon as the pregnancy can be diagnosed or at the instant of a "threatened" abortion, can have any favorable influence. And since we know practically nothing regarding means to improve the germ cells per se, the picture becomes dark indeed.

However, clinical experience and the numerous reports in the literature during the past few years, concerned with the favorable results of treatment of abortion, even though they may be, as Paine<sup>5</sup> says "hardly more than testimonial evidence," must bear considerable weight in our evaluation of the advisability of such treatment. Clinical evaluation is most difficult and beset with many pitfalls, but it is not until enough cases are reported to be of statistical significance that a final judgment of the worth of any method of treatment can be made.

The incidence of spontaneous abortion has been estimated variously by different writers and investigators.

Williams (in 1917) was of the opinion that it was at least one in every five or six pregnancies. Meyer estimated that out of every 100 fertilized ova, only 78 develop to term, the rest being aborted. Taussig,<sup>6</sup> quoting Dr. Kopp's book *Birth Control in Practice*, gives something over 8 per cent of spontaneous abortions in 38,985 pregnancies. In addition, there were 69 per cent of induced abortions, and since it is obvious that a considerable number in this class would have aborted spontaneously if induction had not occurred before this could happen, it is evident that the incidence of spontaneous abortion in this large number of pregnancies would probably have been considerably in excess of 8 per cent.

#### PERSONAL OBSERVATIONS

The following report on the treatment of abortion is based upon a series of 311 consecutive pregnancies, all of which were cared for by me personally in private practice. In these 311 pregnancies, there were a total of 19 abortions, or an incidence roughly of 6 per cent. Six of these abortions were in two patients, who had three each. Some of these cases aborted without treatment and some represent failures in treatment. They are included without differentiation at this point.

This incidence of spontaneous abortion is considerably less than is generally reported. However, all of these women were in comfortable circumstances of life. Almost without exception, they reported early for prenatal care. Adequate diets were insured, with particular attention to proper intake of calcium and other minerals, and vitamins.

quency with which anomalous forms of spermatozoa occur would alone seem to make decidedly venturesome the assumption that there is no such thing as germinal anomalies. In view of the fact that we frankly recognize the occurrence of hereditary anomalies, germinal causes certainly can not be excluded. . . . It is strange that we know so little regarding the anomalous development of the chorion as a factor in the termination of pregnancy. That the cause for the latter not infrequently may be sought in the ovum or spermatozoon one can scarcely doubt, for otherwise one would have to assume that the human reproductive cells are characterized by a unique immunity and perfection."

Corner,<sup>4</sup> in a careful study of the reproductive processes in swine, states, "The question of embryonic pathology in mammals appears less simple the more we learn of the complex factors which control normal development of the embryo. Appearance of a dead or malformed embryo is but the end result of maladjustment somewhere along the intricate mechanisms of fertilization and segmentation, transportation of the embryo through oviduct and uterus, the establishment of placental connections with the maternal organism and the nutrition of the growing embryo. We have not advanced far toward an analysis of these factors in the causation of embryonic mortality. In general, those who approach the question from the standpoint of human embryology lean toward the position of the late Professor Mall, who held that a defective maternal environment, usually in the nature of faulty implantation, is the chief source of morbidity in mammalian embryos, while the geneticists and those embryologists who are familiar with the earliest stages of mammalian development tend to believe that the embryo itself may be the subject of internal defects, which may be hereditary in character or at least may arise during the earliest stages of embryonic existence, or in the germ cells themselves. . . . Summing up these cases of pregnancy examined during the period of implantation, it seems that in the pig there is little evidence that faulty implantation is the cause of embryonic mortality and abnormality, but much to indicate that embryos may become abnormal in spite of a uterine environment which by all the criteria at our command is anatomically and functionally normal. . . . Yet it cannot be claimed that all maternal causes have been ruled out by the type of investigation we have been able to make, however refined the discrimination which we have applied in our microscopic studies. The proof of histological normality does not, for instance, rigidly exclude the possibility of chemical lesions proceeding from altered secretions in the Fallopian tubes and uterus, without visible cytologic change. It is even conceivable that nutritional disorder might alter the uterine environment without detectable change in the endometrium."

The trend has thus been away from environmental factors toward abnormalities in the germ cells themselves as the chief cause for spontaneous abortion. Lethal or sublethal factors, or defects in the genes of the chromosomes, have been found by geneticists in both vegetable and invertebrate material, a particularly exhaustive contribution having been made by Morgan and his co-workers in their investigations on the fruit fly, *Drosophila*. In this fly they have shown that certain combinations of genes in fertilization are incompatible with development of the ovum. Others may be sublethal, and result in defective embryos. Since



experience with it, and experimental evidence by those who have shown its action upon the gravid uterus.

Progesterone was used in 5 mg. doses (intramuscularly in oil) in cases of threatened abortion. If the symptoms were slight, being marked only by slight cramping or slight bleeding or sometimes both, this dose was given once daily. One injection usually resulted in a disappearance of pain in the very early case. If the symptoms were more severe, 5 mg. were given twice daily, frequently for several days. As soon as cramps and/or bleeding ceased, the progesterone was not immediately discontinued. Usually 5 mg. were given every other day for several days. The dose was then reduced with the same interval to 2 mg. This was continued for a week or more, then the intervals lengthened and injections continued for perhaps two more weeks. Unless cramps and/or bleeding were moderate, these patients were not kept at strict bed rest, but came to the office for treatments. Twelve of the patients were hospitalized, not so much for strict bed rest as for the convenience of giving the injections more than once a day, and to have them there if treatment was unsuccessful. I believe that these early spontaneous abortions are definitely upon an endocrine basis, and that normal physical activity has little to do with them, one way or the other.

In those patients with a recurrent abortion history and who were treated prophylactically, progesterone therapy was begun as soon as the diagnosis of pregnancy could be established. Sometimes this was clinically, and sometimes on the basis of a positive Friedman or Aschheim-Zondek test.

If the patient had had two previous abortions, and no successful pregnancy, she was usually given 5 mg. of progesterone three times a week, and that amount daily through the second and third missed menstrual period times. If possible, 5 mg. doses were continued three times weekly through the fourth missed period, then reduced to 2 mg. three times a week. After the fifth month it was given twice a week through the seventh month, when it was usually stopped, although in three cases it was continued beyond this time.

In several instances, in spite of prophylactic treatment as indicated above, there were beginning cramps and/or bleeding at the time these abortions generally occur, viz., between the second and third months. When this happened, the patient was put to bed, one of the barbiturates given, and the frequency of progesterone administration increased. In several instances this was given in 5 mg. doses every four hours for twenty-four hours. In all cases, except the two previously mentioned, whose records are summarized below, the pregnancies were carried to term, with the birth of normal babies.

CASE 1.—L. H., aged 22 years in 1938 when the first pregnancy occurred, had been married for almost four years, without conception. A

Thyroid extract or iodine, as indicated, was frequently given on the basis of either a basal metabolism test or history. Foci of infection were cared for as soon as possible.

If from 50 to 80 per cent of abortuses are pathologic and if the chief cause is defects in the germ plasm, then no somatic factors affecting the mother should make any difference. Few diseases, of whatever severity or chronicity, seem to affect the germ cells themselves, or the fertility of men or women. We know that thousands of women lose their lives yearly because of this fact. If, on the other hand, the maternal environment is a major factor in abortion, all of the factors incident to a comfortable life, as well as treatment directed to the prevention of abortion, ought to make considerable difference. The fact of a low abortion rate in a series of women of this class, together with an apparent considerable success in the treatment of abortion in these women, the fertilized ovum being a fait accompli, would seem to lend confirmatory evidence to the latter view.

In this series of 311 pregnancies, there were 34 "threatened" abortions which were treated. These were manifested by painful rhythmical uterine contractions, or bleeding, or both. In 30, or 82 per cent, the abortion did not occur and the patients were carried to term. Four aborted in spite of treatment. One of these was carried to term in her next pregnancy by prophylactic treatment begun shortly after the first missed menstrual period. The other three were lost sight of.

In addition there were 17 patients who were treated prophylactically from the beginning of their pregnancies. These patients gave a history of having had from one to three previous consecutive abortions, and several of these had been preceded by long periods of sterility before the first pregnancy, or between abortions.

Of these 17 patients, 15 were carried to term the first time such prophylactic treatment was given. All gave birth to entirely normal babies, who continued to develop normally thereafter. This represents a success of 88 per cent in this group of patients, which contained those with a most unfavorable previous reproductive history.

The two failures in this group are the same two who figured in six of the total number of abortions (19) mentioned above, and leaving aside the three patients previously referred to, whom I did not see subsequent to their abortions as primiparas, represent the only two patients in the entire series who were not carried to term, to be delivered of normal babies, either when treated the first time for "threatened" abortion, or the next time, when prophylactic treatment was instituted upon the diagnosis of pregnancy.

In addition to all other measures which should constitute good prenatal care, which have been previously mentioned, the only other agent which was used in the treatment of "threatened" abortion, or in the prophylactic treatment of abortion, was progesterone (proluton, Schering). In no case was morphine used. It is my opinion that morphine has no place in the preventive treatment of abortion and should be used only for pain in inevitable abortion. This opinion is based upon clinical

by which time the pain and bleeding had stopped. The progesterone was gradually reduced over the next several days, and the patient was about her accustomed duties a week later. There were no further signs or symptoms of abortion.

By September, the uterus had enlarged to a much greater extent than justified by the duration of pregnancy, and the fetus could not be definitely palpated, and it continued to grow rapidly over a period of the next three weeks. Diagnosis of polyhydramnios was made. An x-ray picture was made in October, at which time a diagnosis of an anencephalic fetus was reported.

Because of the history of two previous early abortions and the patient's intense desire to have a baby, the fact that fetal movements were daily felt, combined with the faint hope that we might all be wrong in our diagnoses, the pregnancy was not immediately terminated. However, one week later, contractions began, and on admission to the hospital the cervix was dilated about 4 cm. and the membranes were bulging through it. These were ruptured, with the escape of over 7 liters of fluid. Following this, contractions were strong and almost continuous until the delivery about three hours later of a stillborn anencephalic fetus of about seven months. There were also a complete spina bifida and many other skeletal abnormalities.

The uterus contracted well, the blood loss was minimal, and a grossly normal placenta was delivered, which did not show any essential histologic abnormality. Convalescence was uneventful.

Between this patient's second and third pregnancies, a diagnostic curettage was done at the beginning of a menstrual period, and the hyperplasia and secretory changes were excellent. Her thyroid rate had been maintained at a normal level for several years by treatment.

The percentages of success in these two classes of cases, viz., 82 per cent in the treatment of "threatened" abortion, and 88 per cent in the prophylactic treatment, agree closely with that reported by Falls<sup>5</sup> in his treatment of abortion by progesterone of 85 per cent success. As I have stated, clinical evaluation is difficult and I am fully aware that perhaps some of the patients in both of these classes would not have aborted, in spite of contractions or bleeding, or both, if nothing had been done. On the other hand, treatment, such as outlined, has resulted in success far greater than other methods of treatment which I have used in the past.

It is difficult, in the face of clinical results such as these and others which have been reported, to adopt the attitude of helplessness and hopelessness in the problem of spontaneous abortion which would be indicated by reading some of the literature, or particularly to desist in the preventive treatment of abortion through fear that even if successful, babies might be born that were better unborn.

We must agree that some abortions are doubtless due to inherent defects in the germ cells themselves and that these defects may be of a nature which does not permit survival of the ovum or embryo. In such cases it is doubtful if any treatment would result in their survival. Such a case may be represented by "L. H." above. Other defects in the

sterility study was done, with no apparent cause being found for the failure of conception, in either the husband or the wife. Basal metabolic rate was minus 3 per cent, and she was given thyroid extract. Conception followed tubal insufflation test, with one menstrual period intervening. Whether the thyroid or the insufflation had anything to do with this conception, I do not know.

Two and one-half months after the last menstrual period severe cramps began, together with some mbleeding. Five milligrams of progesterone were given. The cramps were markedly reduced in severity for about ten hours, when they recurred with a marked increase in the bleeding. At this time the abortion was considered inevitable and no further treatment was given, except morphine for pain. Abortion was complete in about two hours. No embryo was found in the material passed, and the pathologic report was only of placental tissue.

The next pregnancy was in January, 1940. This was treated prophylactically as outlined above. Bleeding began at the time of the second missed menstrual period, and in spite of increased doses of progesterone, abortion occurred within six hours. Pathologic examination of the abortus showed evidence of hydatidiform changes as described by other authors quoted herein.

The third pregnancy occurred in January, 1942. Prophylactic treatment was not given. Except for marked nausea and vomiting, which responded well to treatment, the pregnancy was uneventful until in March, nine weeks after the last menstruation, when bleeding began. Large doses of progesterone were given, but abortion was complete at ten hours. No embryo was found. This time the villi showed no evidence of hydatidiform changes.

CASE 2.—E. H. had been under treatment, for some time, by an internist for certain allergic manifestations, together with a marked hypothyroidism. She was considerably overweight, and there was a marked generalized hirsutism, especially on the face and neck. Other than this her general structure was typically feminine, as was her voice. Menstrual history was essentially normal.

The first pregnancy dated from May, 1939. Other than routine prenatal care, no treatment was given in this first pregnancy. In July, ten weeks after the last menstrual period, painless bleeding began. Large and frequent doses of progesterone were given, but the bleeding continued actively. Severe cramps began thirty-six hours later, and abortion was complete in twelve more hours.

The next pregnancy began in October, 1940. In addition to the usual prenatal care, she was placed on wheat germ oil and given 5 mg. of progesterone twice a week. This pregnancy was diagnosed early by the Friedman test. In spite of increased doses of progesterone, she aborted during a three-day period in December, 1940, nine weeks after the last menstrual period.

The third pregnancy dated from April, 1941. The usual measures in prophylactic treatment were taken, including vitamin E. The dose of progesterone was increased to 5 mg. three times a week, and daily through the second missed menstrual period. Ten days after this time, slight bleeding and some cramps occurred. She was hospitalized and 5 mg. of progesterone were given every four hours for twenty-four hours,

2. Results of good prenatal care, together with reported successes in the therapeutic and prophylactic treatment of abortion, lend some support to the latter of the causes mentioned above, and at least justify continued efforts in preventive treatment.

3. Progesterone appears to be a valuable adjunct in the treatment of spontaneous abortion.

Proluton was supplied by the Schering Corporation.

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1011 REPUBLIC BUILDING

## USES AND ABUSES OF RADIATION THERAPY IN OBSTETRICS AND GYNECOLOGY\*

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IT WAS in the province of gynecology that radiation therapy was first used to any considerable extent, and in this field it is still one of the most important therapeutic agents. At first radium and x-rays were used almost entirely for the treatment of malignant diseases, because neoplastic growths presented focal aberrations of tissue growth which were tangible entities toward which the rays could be directed. Furthermore, such growths constituted so real a hazard to their hosts that the use of drastic and somewhat experimental therapeutic agents which might destroy them was a justifiable procedure. Experience has taught that not all malignant processes are amenable to such treatment and, moreover, that there are undesirable remote effects which must be taken into consideration. In the application of radiation therapy to gynecologic ailments, there is an increasing volume of advanced malignant disease in the treatment of which radiation is preferable to excisional surgery. In those instances where the malignant disease has passed beyond all help from surgical removal, radiation is frequently the best method of palliative treatment, but, even in these cases, we are finding that radiation must be used with discrimination. It is a misconception,

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germ cells may exist which result in an embryo that may or may not develop to term in utero. Some of these might be aborted if let alone, and it might or might not be possible to prolong their existence, perhaps even to term, by intensive treatment. To do this would obviously be most unfortunate therapy. Case "E. H." above seems to be one of these.

If the views of those who believe that defects in the germ cells are the major cause of spontaneous abortion are correct, then one or the other of two conditions should follow. Either it should not be possible to carry many of those pregnancies to term, or if it is possible, then there should be a great many more abnormal babies born. The most encouraging note in this series of cases is that in not a single instance was a baby born at term that was not in every way normal. One of the abortions figuring in the total of 19 was represented by an hydatidiform mole, and another by the seven months' anencephalic fetus already described.

What the action of progesterone is in these early cases of spontaneous abortion, if it has any specific action, is difficult to say. The great majority of such abortions occur between the second and third months, at the time when placentation is occurring, and the influence of the corpus luteum of pregnancy is waning. I have thought that abortions at this time might be due to a too rapid regression of the corpus luteum, or a delay in the assumption of hormone function by the placenta, resulting in a lowering of the progesterone level below that necessary for a continuation of the pregnancy.<sup>9</sup> Falls and others<sup>7</sup> have reported a diminution or cessation of uterine motility following the administration of progesterone. Bickers,<sup>8</sup> by the same method, however, finds no effect upon the gravid uterus. It is impossible at the present time to reconcile these conflicting results.

We must agree with Paine<sup>5</sup> that what is needed most is some way to diagnose early the inevitable abortion, or the abortion resulting from an abnormal ovum, from those which are fortuitous and which might be prevented by proper treatment. Careful attention to history will frequently make it possible to treat abortion at the most favorable time always to treat it, viz., as soon afterwards as conception can be diagnosed, and many times preferably before conception.<sup>9</sup>

Until increasing knowledge clarifies the causation of spontaneous abortion, clinical experience emphatically justifies our continued efforts to prevent it, both by therapeutic and prophylactic treatment; howbeit in the light of our present knowledge, such efforts will frequently be predestined to failure, and in some cases to unnecessary or unwise treatment.

#### CONCLUSIONS

1. Spontaneous abortion may be due to defects inherent in the germ cells or to maternal environmental factors. Neither cause has been proved to the exclusion of the other. Probably both are concerned.

Even then there is some doubt, as will be shown later, whether radiation therapy has any thing to contribute.

In the second decade of life, the chief indications advanced for radiation therapy are the physiologic malfunctions of the hypophysis, the ovaries, or the uterus. These indications are most frequently represented by infantilism of the genital organs or as scanty, absent, or infrequent menses on the one hand, and excessive bleeding on the other.

From the point of view of the conservative gynecologist, radiation therapy can have little place in the treatment of malfunction of the menses at this period of life. The use of the so-called "stimulating dose" of x-ray or of radium directed toward the hypophysis, the ovaries or uterus must be considered an abuse, because there is almost complete lack of specific knowledge as to what constitutes a stimulating dose, if indeed there be such a thing, and because permanent harm may result, not only to the organs intended to be affected but also to other contiguous structures. Furthermore, the evidence that any permanent good can be expected to result from such treatments is not sufficiently substantiated to be at all convincing.

One hears much of the "temporary castrating" dose of radium or of x-rays. As this application of ray therapy has had fairly common usage, a great deal more is known about it than the so-called "stimulating dose." That the function of the ovaries can be suppressed through the effect of rays upon the Graafian follicle system has been well established. However, to secure this result without producing complete atrophy of the granulosa cells, the dosage must be most carefully graduated according to the age and the habitus of the patient, that is, the younger and thinner the patient, the lower the dose. The computation of the dose and the application of the treatment require great care and exact judgment. These prerequisites are so frequently lacking or are so subject to error that the method is often disappointing and therefore should seldom if ever be used. Indeed, other means of treating the ordinary causes of excessive postpuberal bleeding are so well known and with perseverance are so effectual in almost all cases that one must consider the use of radiation therapy as unnecessary, and more than that, as dangerous because it is fraught with the possibility of permanent infertility and even castration. Until this form of radiation therapy is characterized by a much more accurate knowledge of the dosage received by the ovaries and its effect upon them, both immediate and remote, this application of radium and x-ray should not be used except in very unusual circumstances. We have not felt that it was necessary to resort to its use in a single instance of postpuberal bleeding, always finding that there were adequate means which were less dangerous and more conservative for controlling blood loss.

To summarize, one may say that excepting in the rare instances of malignant disease of the genital tract, it is extremely seldom that a justifiable gynecologic indication for the therapeutic use of radiation therapy can be found in young women under twenty years of age. We should take an active stand in restraining the use of the so-called "stimulating" or "temporary castrating" doses of radium or x-ray as they are often ineffectual or may do permanent damage even when applied under good auspices.

#### THE REPRODUCTIVE PERIOD OF LIFE (THIRD AND FOURTH DECADES)

In dealing with the gynecologic patient of the reproductive age period, the physician must always form his judgments with regard to the use

however, to think of radiation therapy as a technique which may properly be used in the treatment only of malignant disease. As time passes, we learn of new uses in connection with benign conditions. A generation has passed since widespread therapeutic use has been made of radiation therapy, and, while many have evaluated the use of these agents from the point of view of a particular type or group of malignant diseases, there have been few efforts to assess the value of this form of treatment from the more general point of view.

In this consideration, we will not take into account misuses or bad results due to the employment of grossly improper dosages, inadequate filtering of the rays, or lack of diagnostic ability. In order that we may consider the problem on its intrinsic merits, we must assume that the technique of the therapy and the correctness of the diagnosis are satisfactory.

Since the indications for and against radiation therapy in gynecology and obstetrics are influenced considerably by the different phases of life in the woman, they should be regarded, to begin with, from an age period point of view and then evaluated with respect to the various clinical entities, both benign and malignant. The most convenient divisions of the life span for this purpose are:

- |                            |                              |
|----------------------------|------------------------------|
| 1. Pre- and postpuberal    | (First two decades)          |
| 2. Reproductive            | (Third and fourth decades)   |
| 3. Pre- and postmenopausal | (Fifth and Sixth decades)    |
| 4. Senescence              | (Seventh and eighth decades) |

#### PRE- AND POSTPUBERAL PERIOD (FIRST TWO DECADES)

The use of roentgen rays or of radium for the treatment of gynecologic dyscrasias in the first decade of life should be confined to the treatment of the rare instances of malignant disease. These are usually the embryonal types of epithelial or connective tissue tumors. Unfortunately, malignant tumors in the young are rarely diagnosed early enough or found in a sufficiently advantageous position to permit surgical excision. The occasional exception to this statement is the infrequently encountered malignant dysgerminoma. When this tumor is found, the indication is considered to be excisional surgery, aided by the use of x-rays or radium therapy. Although few persons have seen enough of these tumors to justify any very definite attitude toward their treatment, the consensus of opinion seems to be that they should receive radiation treatment. In addition, the granulosa cell tumor of the ovary should be mentioned as it is occasionally found in the first decade of life and is most often associated with precocious puberty. There has been much misconception concerning the significance of this growth, largely because it has been indiscriminately called "granulosa cell carcinoma," a term which, of course, implies malignant characteristics. This misleading nomenclature is unfortunate, for most granulosa cell tumors are benign, in fact, less than 20 per cent develop malignant characteristics. Radiation therapy, if it is to be used, must therefore be applied only to those patients from whom a granulosa tumor has been removed which has definitely malignant histologic features.



gression of the pathologic process. However, more often than not, the ovarian tissue already damaged by the endometrial cyst formations will lapse into permanent abeyance of function when treated with even small doses of x-ray or radium. The more specific approach with the scalpel is therefore to be preferred, at least in the initial stage of treatment. This is particularly true because laparotomy will usually be necessary to confirm the diagnosis, at which time appropriate excisions can be carried out. However, any remaining ovarian tissue, which should be left in the young woman whenever possible, will often produce enough hormone to allow the continued growth of the endometrial process. It may be, therefore, that as a sequel to the laparotomy one may elect to use radiation therapy rather than to resort to a second or third laparotomy. Under such circumstances, castration by radiation even in relatively young women may be a highly conservative procedure.

Similarly the use of castration in treatment of carcinoma of the breast in women of reproductive age may be warranted, as there is very good evidence that not only normal mammary duct and alveolar epithelium are stimulated to growth by the hormonal products of the ovary but that the malignant cells of the same origin may respond in a similar manner. This therefore constitutes another exception to the conservative attitude which is well indicated.

It has been found that therapeutic abortion may be induced in the early stages of pregnancy by means of x-ray radiation. A sufficient dose, when directed toward the site of implantation in the uterus, brings about degeneration of the trophoblastic ectoderm, followed by death of the fetus and subsequent expulsion of the product of conception. Use of the method has been urged by some enthusiasts, chiefly because they claim it to be devoid of blood loss and that the dangers of infection may be greatly reduced. However, abortion produced by x-ray is at best an awkward procedure, because the product of conception is retained in utero for some time after death, and the procedure seems to lack sufficient advantage over other more prompt methods to recommend its widespread use. But even more important is the inescapable danger of radiation effects upon the ovaries; this probability is sufficient to condemn the method unless simultaneous castration is desired, which will infrequently be the case.

When carcinoma of the cervix or of the ovaries coincides with pregnancy, as it does very occasionally, it is wise usually to evacuate the uterus before attempting to give radiation therapy. Adequate x-ray therapy for carcinoma will either kill the fetus in the early stages of pregnancy or produce serious malformation, because the direct beam as well as the scattering of the rays must necessarily affect large portions of the body of the fetus. Radium, on the other hand, may not do so because it may be more locally applied and because the dosage decreases rapidly with each successive centimeter that it is placed away from susceptible tissues.

The treatment of myomas by means of radium or x-rays has been widely used, so that the advantages and handicaps of the method can be fully evaluated. Those who have had wide experience in the use of radiation for this purpose lay down the following criteria which must be fulfilled if this means of treatment is to be carried out without undesirable complications:

1. The size of the growth must not be over 12 cm. in diameter.
2. The growth must be fairly symmetrical or globular in shape.

of therapeutic agents being guided by a sensitive appreciation of the importance of preserving the procreative function. Any form of treatment directed toward the cure of an ill which, at the same time precludes the possibility of childbearing, can only be justified when the dangers inherent in the disease are of such a magnitude as to fully warrant castration. The interpretation of that phrase "fully warrant" is necessarily vague and will differ greatly in many minds, having different backgrounds of training, temperament, and modes of thought.

Approaching the diseases of the reproductive period of life in which radiation therapy may be applied from this point of view, it is at once apparent that aside from those of a malignant nature there can be no wide use for radium and x-ray until the end of the period is approached or actually reached.

The use of the "stimulating dose" of x-ray applied to the pelvic fields to overcome sterility has been urged by some, and a few series of apparently successful cases have been reported in the literature. However, such experiments, for such they are, are inadequately controlled so that one cannot state with any degree of assurance that the radiation therapy was of substantial benefit. There is no indication, either clinically or experimentally, that x-rays or radium ever exert a stimulating effect. Also, we are left in complete ignorance as to immediate and remote damage that may have been sustained by patients so treated. It is obvious, therefore, that this is not a form of therapy which in its present state can be more than very sceptically accepted by a wise profession.

We should also point out that the use of penetrating rays for therapeutic purposes has not been in vogue for a long enough time to permit a complete knowledge of their very remote effects. It is quite possible that succeeding generations begotten by patients who have received x-ray and radium therapy may reveal inherited deficiencies of the germ plasm as a result of that treatment. The basis for calling attention to this possibility lies in the experimental work which has been done on drosophilia, mice, and guinea pigs, which demonstrates beyond a doubt that in these animals the effect of radiation may be transmitted and appear two, three, or even four generations later in the form of abnormal developments of the extremities, resulting in partial or complete absence of arms or legs or with clubbed feet, as well as occasional abnormal pigmentation of the skin surfaces.

The attitude toward "temporary castration" should, we believe, be the same in this as in the earlier periods of life, because it cannot be adequately controlled and hence should not be applied unless, when as at the end of the childbearing period, one may be willing to accept complete castration, should this be the inadvertent result. Under the latter circumstances, the full castration dose will usually be preferable to a lesser one if the indication is really adequate for the use of this therapeutic agent.

Endometriosis may be one of the exceptions to the foregoing statement. This benign disease occurs with some frequency in women twenty-five or more years of age. As is well known, it may and often does destroy fertility. The pathologic process is dependent upon and is promoted by ovarian hormones coming largely from the maturation of the Graafian follicle. In these patients one occasionally may be warranted, in an effort to suppress ovarian function for a period of several months, to remove or decrease the stimulating hormones and thus to induce re-

menopause and afterward, but to point out that the use of even the most superficial x-ray treatments to this region is not wise except perhaps in such small amounts as 75 r. for five treatments, for though they may give relief of the discomfort, they frequently are followed at a later time by abnormal skin changes closely analogous to kraurosis. This presumably is due to endarterial changes induced in the cutaneous capillaries which cause them to undergo gradual occlusion with consequent decrease in the blood supply.

#### THE USE OF RADIUM AND X-RAY IN THE TREATMENT OF MALIGNANT NEOPLASMS

Carcinoma of the vulva should never be treated by any form of radiation therapy, because doses sufficient to eradicate the cancer will result in fibrosis and other late manifestations which are undesirable. The perineum is notably the most intolerant skin surface of the body to radiation therapy. The only treatment is excision of the local lesion followed by dissection of the inguinal nodes. However, after operation, radiation of the inguinal region only has been recommended by some; on the other hand, many radiologists would advise against its use in this way.

From what has been said it is obvious that while radiation therapy has definite uses in nonmalignant states, it is with malignant conditions that its use should be chiefly concerned. This will remain true until the many undesirable side effects can be eliminated completely or at least minimized to a much greater extent than present techniques make possible. With cancer, however, it has proved to be a great boon to women when surgery is out of the question because of general debility, or when the neoplastic disease has advanced beyond the stage where excision is possible. This is true because cancerous processes in themselves constitute such an extreme hazard that the use of a drastic agent with its frequently undesirable side effects is indicated. There undoubtedly will be striking advances in techniques for the employment of the various forms of radiation therapy in the future as there have been in the past. As a result, the cure rate should be appreciably increased with a diminution in disadvantageous secondary effects. The past twenty years have seen notable advances in this direction. One of the most important recent improvements has been the application of deep x-rays directly to the cervix and parametria by means of the intravaginal cone. We have seen most encouraging regression following this technique.

Despite these real advances in radiation therapy and the others which may be forthcoming, there is urgent need for an entirely different approach to the problem of gynecologic cancer. Instead of waiting until the woman presents herself with the disease, the attitude of gynecologists should be one of aggressive prophylaxis. By that it is meant that we should obtain such a thorough follow-up of all women patients in the cancer-bearing period that we would thereby detect malignancy of the genital tract in its incipency when it can be treated and more frequently cured, not by radiation alone, but by a large variety of relatively simple and inexpensive means. This may sound somewhat Utopian, but much would be accomplished if every obstetrician and gynecologist applied the same general principles to the postreproductive care of women that are now in vogue during pregnancy and commonly

3. Pedunculated tumors cannot be safely treated, as they may undergo rapid degeneration due to precarious blood supply and produce adhesions, obstructions, etc.

4. Submucous tumors are contraindicated because of the dangers of becoming infected.

5. Rapidly growing tumors may be sarcomatous and this form of malignancy is notoriously resistant to radiation therapy.

6. There must be no inflammatory involvement of the adnexal organs.

7. Myomas undergoing degenerative changes are not suitable.

To the foregoing we should add that the tumor must produce symptoms such as bleeding or mechanical disturbances.

This, all will agree, is a rather formidable list of contraindications which in themselves, if present, would leave only a small number of suitable cases. But if in addition one asks how can one be sure that they are fulfilling these conditions, except by means of exploratory operation, it would seem at once to the trained surgeon that operative removal is by all odds the procedure of choice except in a few patients near the menopause with small and suitably placed tumors in whom ovarian conservation is not essential, or in patients who because of other diseases are not fit candidates for operation. In short, it would seem that there are only a very few instances of myomatous uterus that could not be treated better by surgical excision than by radiation.

The treatment of carcinoma of the cervix constitutes the greatest use which can be made of radiation during the reproductive period of life. That it has been a great aid and that it is the best mode of therapy in all stages of this disease, excepting the very earliest, is unquestionable. More will be said later on this subject.

#### PRE- AND POSTMENOPAUSAL PERIOD (FIFTH AND SIXTH DECADES)

As the menopause is approached, the desirability or possibility of childbearing having largely or completely passed, that is, in women forty or more years of age, the indications for the use of radium and x-ray in the treatment of benign conditions increase. Hyperplasia of the endometrium when it does not yield to curettage or hormonal treatment, endometriosis, the submucous myoma which produces excessive blood loss, and adenomyoma all may be treated efficiently and with the obviation of laparotomy by means of radiation. Here, contrary to the usage of many, x-ray may be preferable to radium. Intracavitary radium in 1,400 to 1,600 mg. hour doses is quicker and in many instances satisfactory. However, when there is danger of infection in the uterus or adnexal organs, and there frequently is such danger, the deep x-ray treatments are distinctly preferable. If the myomas are large enough to produce crowding of the pelvic organs and thus instigate pressure symptoms, it is very doubtful whether any form of radiation will prove a satisfactory solution. In these instances, even though the menopause, with its cessation of ovarian function and, hence with a recession of the growth stimulus, is imminent, and even though, as is well known, there may be and usually is a diminution in the size of the tumors, laparotomy with surgical excision of large tumors will nearly always prove to be the most satisfactory mode of attack.

The treatment of pruritus of the vulva and anal region should be mentioned, not only because of the frequency of these ailments at the

definitely be refused even palliative radiation treatment and will be given comforting drugs instead. In short, it is a great mistake to conclude that *all* patients with inoperable or recurrent cancer should receive radiation therapy, for often more harm than good is done.

Cancer of the cervix and that of the fundus of the uterus is well recognized and the various types are quite well differentiated (thanks to Martzloff, Schultz, and others who have devoted specific study to these lesions). In contrast, cancer of the ovary is not in such a well-ordered state of recognition, and therapeutics is discouraging, probably because the etiology and potential variations are much more complicated. Carcinoma of the ovary is a very common disease which, though varied in form and difficult to treat, should, we think, be accorded better therapy than it commonly receives. It is rather disappointing to read paper after paper on ovarian cancer coming, as many of them do, from good hospitals without anything like an adequate attempt at a critical analysis of the different histologic varieties of growth. The unqualified term, "ovarian carcinoma" means almost nothing beyond the mere fact that the process possesses the characteristics usually ascribed to malignant diseases. The life cycle of the different ovarian malignancies as well as their potentialities for harm are so varied as to require not only individualized consideration but widely divergent therapy.

A knowledge of the life cycle of the ovarian tumors and of their sensitiveness to radiation therapy is a definite prerequisite to the treatment of these lesions. Indeed, we need not confine this statement to ovarian neoplasms; it is equally true of all tumors of the female genital tract. Radiation treatment of the common forms of malignant neoplasm of the ovary, that is, the serous cystadenocarcinoma and the pseudomucinous cystadenocarcinoma, are most discouraging, particularly when the papillary processes have implanted themselves upon the serous lining of the abdomen and its viscera, if a cure of the disease is anticipated. However, deep x-ray therapy may and often does produce a temporary reduction in size of the tumor masses together with a decrease in the rate at which ascitic fluid is produced, so that the use of the deep x-ray may be helpful in making an inoperable tumor one which can be removed, as well as affording comfort to the patient for a period of months by diminishing abdominal distention due to ascitic fluid. On the other hand, cure by any means is rare.

#### SUMMARY

In conclusion, we may say that radiation therapy is very often a blessing, but it may also be a curse. Its use must be guided by clinical discretion and extensive knowledge of neoplastic and benign disease processes. The enthusiasm of radiation specialists is essential to the development of the art of radiation therapy; however, the application must be held within the bounds deemed suitable by conservative clinicians whose experience and long range point of view, in consultation with the radiologist, should dictate its use and decide upon appropriate application. In addition, let us again emphasize that the mere treatment of well-established or hopeless malignant processes by radiation and all other means is but to beg the question as far as the responsibilities and capabilities of the profession are concerned. Great ad-

known as antenatal care. If semiannual physical examinations by competent gynecologists were available to cancer-susceptible women to the same degree that medical care is now available during pregnancy, we could, in a few years change the whole complexion of cancer therapy as far as the female generative tract is concerned.

This lack of constant and competent gynecologic observation of women in the cancer age constitutes the greatest omission of which our branch of the medical profession may be said to be guilty. This situation should be and, it is to be hoped, will be changed in the near future. An informed and well-trained staff of gynecologists should bring about the adequate training of physicians in sufficient numbers to make it possible to carry out such a program of cancer prophylaxis through semiannual examinations of women from the age of thirty-five to sixty or more years of age. Then and only then will we begin to meet the challenge of gynecologic cancer, because such observation is the only way in which the *early stages* of the disease may be detected.

#### RADIATION THERAPY IN THE AGED WITH ADVANCED STAGES OF MALIGNANCY

With what has seemed to be an increased incidence of advanced malignancy of all types occurring in women and with greater realization of the value of radiation therapy as contrasted to surgical treatment in the treatment of such patients, there has been an evergrowing tendency to refer all patients who are hopelessly ill with cancer to the roentgenologist for radiation treatment.

Sometimes marked regression of the malignant process results from treatment, or pain is greatly relieved. Thus the final days of the patient are not only made more comfortable but they may even be increased in number. (Such a result is not only desirable but it is the duty of the doctor to secure it for his patient if this is at all possible.) Unfortunately, however, the outcome is not always so fortuitous even under the best auspices. Frequently, instead of giving comfort and prolonged life, radiation produces nausea, vomiting, and added pain to such a degree as to constitute an augmented burden and make further life definitely less desirable to the patient. X-ray treatment of desperately ill or very aged patients with extensive metastatic disease is to be deplored with very few exceptions. It is much better, though the decision be a difficult one, to avoid the use of radiation in many such patients, because life under an increased burden of suffering may not be worth while if more discomfort is to be the lot of the patient. Furthermore, it is unfair to the radiologist to insist on radiation treatment only because the physician or the family are, so to speak, "grasping at last straws." The correct procedure should be to determine as accurately as may be possible the nature and extent of the malignant disease process, after which a consultation with the radiologist should take place in which the situation in the particular patient and in similar cases should be discussed, and the possible advantages and disadvantages thoroughly considered. Some patients will then be given radiation treatment carried out to an adequate degree to secure remission or palliation. Others, a border line group, will be treated tentatively with a trial of therapy to observe how the patient in general and the tumor specifically react to the treatment. If the response is found satisfactory, the treatment may be continued; on the other hand, when the response is poor the therapy should be stopped. Still other patients will

TABLE I.\* KINDS AND APPROXIMATE QUANTITIES OF FOOD PER WEEK (FOR PREGNANT WOMEN)

|                           | MILK†<br>QT. | POTATOES,<br>SWEET<br>POTATOES<br>LB.-OZ. | DRIED BEANS,<br>PEAS, AND<br>NUTS<br>LB.-OZ. | TOMATOES,<br>CITRUS<br>FRUIT<br>LB.-OZ. | LEAFY,<br>GREEN,<br>YELLOW<br>VEGE-<br>TABLES<br>LB.-OZ. | OTHER<br>VEGE-<br>TABLES<br>AND FRUIT<br>LB.-OZ. | EGGS<br>NO. | LEAN MEAT,<br>POULTRY,<br>FISH<br>LB.-OZ. | FLOUR,<br>CEREALS<br>LB.-OZ. | FATS<br>LB.-OZ. | SUGARS<br>LB.-OZ. |
|---------------------------|--------------|---|--|---|--|--|-------------|---|------------------------------|-----------------|-------------------|
| Low-cost<br>adequate      | 7½           | 3-0                                       | 0-6  | 2-0                                     | 3-0  | 2-0  | 6           | 1-12                                      | 2-12†                        | 0-12            | 0-12              |
| Moderate cost<br>adequate | 7½           | 1-12                                      | 0-2  | 2-0                                     | 4-0  | 4-8  | 6           | 2-8                                       | 2-2                          | 1-0             | 1-0               |
| Liberal                   | 7            | 1-6                                       | 0-2  | 6-0                                     | 4-0  | 6-0  | 9           | 2-8                                       | 1-8                          | 1-2             | 1-2               |

\*These quantities are translated into household terms under separate headings below.

†Or its equivalent in cheese, evaporated milk, or dried milk.

‡To meet iron allowances, from 30 to 50 per cent of the cereal should be whole grain.

vances will be realized when there is such a thorough and capable application of the prophylactic idea that we shall have the problem of treating genital cancer in its incipency rather than in its advanced stages. Such a program is not premature or in the least an unbridled phantasy; all that is lacking is a full appreciation by the profession of the simple methods by which such a program may be realized, and the zeal necessary for their appreciation.

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## NUTRITION STUDY IN PREGNANCY\*

### FOOD HABITS OF 514 PREGNANT WOMEN

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THE food intake records of 514 pregnant women in Philadelphia were analyzed and recently reported.<sup>1</sup> The women represented several population, economic, racial, and nationality groups.

The diets, when compared with the recommended allowances of the National Research Council, were much below the standards for pregnancy. The average diet was 20 per cent below the allowance in calories, 22 per cent in protein, 53 per cent in calcium, 33 per cent in iron, 55 per cent in vitamin A, 43 per cent in vitamin B<sub>1</sub>, 47 per cent in ascorbic acid, and 50 per cent in riboflavin. Ten (2 per cent) diets could be termed good, 209 (41 per cent) fair, and 295 (57 per cent) poor. Calcium deficiency was the fault most constantly encountered.

When the food intake records were analyzed, no cognizance was taken of the specific foods which the women ate. A consideration of their food habits is the purpose of this report.

Weekly food consumption was compared with those amounts recommended for pregnant women in the pamphlet, *Planning Diets by the New Yardstick of Good Nutrition*, a publication of the Bureau of Home Economics. The weekly diet plans for pregnant women at three levels of cost, showing the food classifications, are shown in Table I.

### FINDINGS

*Milk.*—Milk makes many important contributions to the diet, the most notable of which is calcium. It also provides phosphorus, protein of good quality, vitamin A, thiamin, and riboflavin. It is a relatively cheap food and a wise purchase. Translated into servings, all three diet plans would indicate the daily use of at least one quart of milk to drink, in cooked food, or as cheese. Milk consumption in the group studied is shown in

\*This study was made under a grant from the Selina B. McIlhenny Fund for Clinical Investigation in the Presbyterian Hospital in Philadelphia.



The diet of the pregnant woman should contain at least one serving daily of these foods and two if the food budget will permit. Table V shows that a small percentage of the group ate two servings daily. A large number consumed vitamin C foods less frequently than once daily.

*Leafy, Green, and Yellow Vegetables.*—All fruits and vegetables make outstanding contributions to the diet in the way of minerals and vitamins. They help to maintain alkaline reserve, they provide roughage, and they lend color, flavor, and texture to menus. They are not always cheap, and transportation factors affect their cost.

TABLE VI. LEAFY, GREEN, AND YELLOW VEGETABLES

| SERVINGS                      | NUMBER OF WOMEN | PER CENT |
|-------------------------------|-----------------|----------|
| None                          | 5               | 1        |
| Some, but less than one daily | 231             | 45       |
| One, but less than two daily  | 213             | 41       |
| Two or more daily             | 65              | 13       |

Leafy, green, and yellow vegetables are important for their iron and vitamin A content. Pregnant women limited to low-cost diets should use them about once a day and those who can afford the moderate cost and liberal diets should have one or two servings daily. Note how few women attained the desire of two servings (Table VI). Almost one-half of these women were in the highest income groups. Those who had none were in the lowest.

*Other Vegetables and Fruits.*—To use the quantities of other fruits and vegetables not mentioned above and suggested in Table I, women in the low-income group should eat them about once daily. Those in the moderate group should have about two servings a day. Those in the liberal group should eat two or three servings daily. Table VII explains how the women in this study met the standards. More than one-half of those eating only one serving daily were in the low income group.

TABLE VII. OTHER VEGETABLES AND FRUITS

| SERVINGS                       | NUMBER OF WOMEN | PER CENT |
|--------------------------------|-----------------|----------|
| None                           | 5               | 1        |
| Some, but less than one daily  | 139             | 27       |
| One, but less than two daily   | 199             | 39       |
| Two, but less than three daily | 113             | 22       |
| Three or more daily            | 58              | 11       |

*Eggs.*—Eggs contain protein, they are excellent sources of vitamin A and iron, and they provide other minerals and vitamins as well. One egg in some form should be included about once a day in the pregnant woman's diet and more often when food money is not limited. Not many of these women used one egg daily (Table VIII).

TABLE VIII. EGGS

| SERVINGS                                | NUMBER OF WOMEN | PER CENT |
|---|-----------------|----------|
| None                                    | 54              | 11       |
| Some, but less than one every other day | 214             | 42       |
| 3½ per week, but less than 7            | 177             | 34       |
| One daily or more                       | 69              | 13       |

*Lean Meat, Poultry, and Fish.*—In addition to their protein value, these foods are rich in thiamin, riboflavin, and nicotinic acid. Liver and

TABLE II. DAILY CONSUMPTION OF MILK

| DAILY                          | NUMBER OF WOMEN | PER CENT |
|--------------------------------|-----------------|----------|
| Some, but less than 8 ounces   | 131             | 25       |
| 8 ounces, but less than 1 pint | 198             | 39       |
| 1 pint, but less than 1 quart  | 172             | 33       |
| 1 quart                        | 13              | 3        |

Table II. A very small percentage consumed one quart or more daily. About one-half of this group was made up of women in the highest income brackets. The average was less than one pint daily.

*Potatoes and Sweet Potatoes.*—Potatoes furnish calories at low cost. They are good sources of vitamin B<sub>1</sub>, vitamin C, and iron. Sweet potatoes are particularly valuable for their vitamin A content.

The recommendations in Table I would amount to two servings daily for the low-cost diet, one or two for the moderate-cost diet, and one for the liberal diet. Fifteen women, most of whom were in the low income group, used potatoes at least twice daily (Table III).

TABLE III. POTATOES AND SWEET POTATOES

| SERVINGS                      | NUMBER OF WOMEN | PER CENT |
|-------------------------------|-----------------|----------|
| None                          | 14              | 3        |
| Some, but less than one daily | 311             | 60       |
| One daily, but less than two  | 174             | 34       |
| Two or more daily             | 15              | 3        |

*Dried Beans, Peas, and Nuts.*—Legumes, generally, are valuable for protein, iron, and thiamin. They also furnish calories cheaply. They should be used four times weekly in the low-cost diet, three times weekly in the moderate-cost diet, and once weekly in the liberal diet.

Almost one-half the number of women studied used no legumes at all. About two-thirds of those who used them at least four times weekly were in the lowest income group (Table IV).

TABLE IV. DRIED BEANS, PEAS, AND NUTS

| SERVINGS                       | NUMBER OF WOMEN | PER CENT |
|--------------------------------|-----------------|----------|
| None                           | 246             | 48       |
| Some, but less than two weekly | 188             | 37       |
| Two or three weekly            | 59              | 11       |
| Four or more weekly            | 21              | 4        |

*Tomatoes, Citrus Fruit or Other Vitamin C Rich Foods.*—Those fruits and vegetables which are good sources of vitamin C can usually be relied upon to furnish other vitamins and minerals as well. Since they may be eaten raw or after short cooking periods, there is not much danger of losing their vitamin content.

TABLE V. TOMATOES, CITRUS FRUIT OR OTHER VITAMIN C RICH FOODS

| SERVINGS                      | NUMBER OF WOMEN | PER CENT |
|-------------------------------|-----------------|----------|
| None                          | 12              | 2        |
| Some, but less than one daily | 202             | 39       |
| One daily, but less than two  | 214             | 42       |
| Two or more daily             | 86              | 17       |

Only 59 per cent of them chose one serving or more of citrus fruits and vitamin C rich foods daily.

Only 54 per cent ate at least one leafy, green, or yellow vegetable daily.

A large number of women did not realize the need in the diet for potatoes, legumes, and other vegetables and fruits not mentioned above.

Only 47 per cent consumed three or four eggs weekly.

Twenty per cent reported an intake of lean meat, poultry, and fish of one and one-half servings daily.

Seventeen per cent ate one-half of their bread and cereals in the whole grain form.

Only about 21 per cent used one ounce of butter or fortified butter substitute daily.

The authors are indebted to Mrs. Anna dePlanter Bowes, Dr. Esther F. Phipard, and Dr. E. D. Burdick for their helpful suggestions.

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2206 LOCUST STREET

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## POSTMENOPAUSAL ENDOMETRIOSIS

### A CASE REPORT AND REVIEW OF THE LITERATURE

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IT IS insufficiently emphasized in the literature on endometriosis that typical lesions are not infrequently found in women past the menopause. The existence of a sizable group of noncyclical women presenting these lesions deserves consideration, because one might not predict such a group from accepted concepts of the pathogenesis of the disease and further, because the origin and fate of such tumors are of concern in prognosis and treatment of these patients.

Pathologic diagnosis of the lesion depends on the demonstration of epithelial elements closely resembling endometrium, in an abnormal location. Many theories have been advanced to account for the presence of this ectopic tissue, and, although each seems to explain certain clinicopathologic observations, the accumulated body of evidence contains data irreconcilable with any single theory. This suggests that no single mechanism is universal in the pathogenesis of this disease. Whether, however, one attributes the genesis of the lesion to (a) diverticular invasion of the uterus by normal endometrium (Cullen), (b) activation of celomic rests (Iwanoff, Novak), (c) epithelial heterotopy dependent

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lean meat are high in iron content, and liver is an excellent source of vitamin A. All add interest and flavor to the diet.

To meet dietary requirements, pregnant women should have one serving of these foods every other day in the low cost group, one serving daily in the moderate cost group and at least that much and preferably more in the liberal group. Most of these women had at least one serving every day (Table IX).

TABLE IX. LEAN MEAT, POULTRY, AND FISH

| SERVINGS                      | NUMBER OF WOMEN | PER CENT |
|-------------------------------|-----------------|----------|
| None                          | 1               | (-.2)    |
| Some, but less than 3½ weekly | 19              | 4        |
| 3½, but less than 7 weekly    | 149             | 29       |
| 7, but less than 10½ weekly   | 243             | 47       |
| 10½, but less than 14 weekly  | 81              | 16       |
| 14 or more weekly             | 21              | 4        |

*Flours and Cereals.*—No attempt was made in this report to measure the amounts of bread and cereal consumed. The interest was centered instead on the amount of whole grain cereals and bread. These are important for their vitamin B and iron content. Table X shows how infrequently these women ate at least one-half of their bread and cereals in the whole grain form.

TABLE X. WHOLE GRAIN CEREALS AND BREAD

| AMOUNT                          | NUMBER OF WOMEN | PER CENT |
|---------------------------------|-----------------|----------|
| None                            | 107             | 21       |
| Some, but less than ½ of intake | 317             | 62       |
| ½ or more of intake             | 90              | 17       |

*Fats.*—Table XI shows how many women used one ounce or more of butter or fortified oleomargarine daily. Butter is important for vitamin A as well as for the calories it yields. Some women, most of whom were private patients, used cod-liver oil routinely during pregnancy.

TABLE XI. BUTTER AND FORTIFIED OLEOMARGARINE

| AMOUNT                              | NUMBER OF WOMEN | PER CENT |
|-------------------------------------|-----------------|----------|
| None                                | 20              | 3.9      |
| Some, but less than one ounce daily | 383             | 74.5     |
| One ounce or more daily             | 111             | 21.6     |

*Sugars.*—Molasses, honey, brown sugar, and unrefined syrups are to be desired over refined sugar. Only 63 women (12 per cent) used the unrefined forms of sugar.

A study of the food habits of 514 pregnant women in Philadelphia reveals principally a lack of knowledge of adequate food values. A slight effort on the part of obstetricians in nutrition education for pregnant women would bring about good results not only for the mother and fetus, but for the entire family as well.

## SUMMARY

Only 3 per cent of the women in this group consumed one quart of milk daily. Twenty-five per cent of them had less than 8 ounces daily.

TABLE I. ASSOCIATED PATHOLOGY IN 203 CASES OF ADENOMYOSIS

| LESION                                | NUMBER OF CASES | PERCENTAGE |
|---------------------------------------|-----------------|------------|
| No associated lesion                  | 21              |            |
| Uterine lesions                       | 158             |            |
| Fibromyoma                            | 148             | 73.0       |
| Myosarcoma                            | 3               | 1.5        |
| Carcinoma                             | 2               | 1.0        |
| Hematometra with cervical stricture   | 1               | 0.5        |
| Double uterus                         | 1               | 0.5        |
| Normal pregnancy                      | 1               | 0.5        |
| Hydatid mole, chorioadenoma destruens | 1               | 0.5        |
| Chorioepithelioma                     | 1               | 0.5        |
| Endometrial lesions                   | 54              |            |
| Hyperplasia                           | 26              | 13.0       |
| Polyp                                 | 28              | 14.0       |
| Ovarian lesions                       | 74              |            |
| Follicular cyst                       | 44              | 22.0       |
| Chocolate cyst                        | 9               | 4.5        |
| Simple cyst                           | 9               | 4.5        |
| Serous cyst                           | 3               | 1.5        |
| Dermoid cyst                          | 3               | 1.5        |
| Papillary cyst, serous                | 2               | 1.0        |
| Papillary cyst, pseudomucinous        | 2               | 1.0        |
| Theca cell tumor                      | 1               | 0.5        |
| Granulosa cell tumor                  | 1               | 0.5        |
| Miscellaneous                         | 11              |            |
| Endometriosis of tube                 | 5               | 2.5        |
| Parovarian cyst                       | 3               | 1.5        |
| Endometriosis of pelvic peritoneum    | 1               | 0.5        |
| Endometriosis of abdominal wound      | 1               | 0.5        |
| Endometriosis of appendix             | 1               | 0.5        |

TABLE II. ASSOCIATED PATHOLOGY

| AUTHOR                            | NO. CASES OF<br>ENDOMETRI-<br>OSIS IN<br>SERIES | PERCENTAGE CO-INCIDENCE     |                     | FIBROIDS |
|-----------------------------------|---|-----------------------------|---------------------|----------|
|                                   |   | HYPERPLASTIC<br>ENDOMETRIUM | FOLLICULAR<br>CYSTS |          |
| Waters <sup>18</sup>              | 18  | -                           | -                   | 33       |
| Witherspoon <sup>20</sup>         | 44  | 90                          | 100                 | -        |
| Henderson <sup>13</sup>           | 82  | 24.3                        | -                   | 21       |
| Jeffcoate <sup>14</sup>           | 113   | 71                          | -                   | 41       |
| Allen <sup>1</sup>                | 112   | 70                          | -                   | -        |
| King <sup>15</sup>                | 114   | 50                          | -                   | 52       |
| Smith <sup>17</sup>               | 159   | 42                          | -                   | -        |
| Dreyfuss <sup>4</sup>             | 162   | 29                          | -                   | 54       |
| Bland <sup>2</sup>                | 172   | -                           | -                   | 41       |
| Fallas and Rosenblum <sup>5</sup> | 260   | 10.7                        | 3                   | 54       |
| Counsellor <sup>3</sup>           | 884   | -                           | -                   | 73       |
| This series                       | 203   | 13                          | 22                  |          |

TABLE III. AGE DISTRIBUTION

| AUTHOR                            | NO. OF<br>CASES | UNDER 20 | 20-40 | 40-50 | OVER 50 | %<br>OVER 50 |
|-----------------------------------|-----------------|----------|-------|-------|---------|--------------|
| Dreyfuss <sup>4</sup>             | 152             | 0        | 43    | 96    | 13      | 8.6          |
| Fallas and Rosenblum <sup>5</sup> | 260             | 0        | 139   | 102   | 20      | 8.0          |
| Bland <sup>2</sup>                | 276             | 1        | 139   | 110   | 26      | 9.6          |
| Counsellor <sup>3</sup>           | 884             | 0        | 333   | 443   | 108     | 12.2         |
| This series                       | 203             | 0        | 75    | 107   | 21      | 10.3         |
| Total                             | 1,775           |          |       |       |         |              |
| Average                           |                 |          |       |       |         | 10.6         |

on inflammatory or hormonal stimulus (Meyer), (d) lymphatic or hematogenous spread (Halban), or (e) retrograde tubal menstruation (Sampson),\* it seems logical to concede that its subsequent growth and invasiveness are dependent on the same hormonal influences on which the growth of normal endometrium is contingent. The lesion, as observed in the cyclical woman, is characterized by symptoms indicating cyclical growth activity, and by the histologic pictures of proliferation and edema, desquamation and hemorrhage, closely paralleling the changes of the normally situated endometrium. Moreover, endometriosis before the menarche is exceedingly rare.

Not only does hormonal stimulation appear to be necessary for the growth of these tumors, but evidence of hyperestrinism is to be found in a large proportion of these patients, as previous authors have argued.<sup>14, 19</sup> In the absence of laboratory data, the evidence on this point rests on the coincidence of endometriosis with endometrial hyperplasia and follicular cysts, lesions which are probably related to hyperestrinism. Uterine fibromyomas, also possibly related to endocrine causes, are, similarly, quite frequently associated.

We have reviewed the records of all cases of uterine endometriosis (adenomyosis) surgically treated in this hospital during the nine-and-one-half-year period from January, 1933, to July, 1941, with special attention to the age, menstrual status, symptomatology, and associated pathology. An analysis of the associated findings in the 203 cases (Table I) reveals a statistically significant incidence of the above-mentioned lesions; much in excess of that to be expected were these lesions and endometriosis etiologically independent. This finding is in qualitative agreement with those of other reviewers (Table II).

The above considerations make it reasonable to conclude that the growth and maintenance of ectopic endometrial foci are dependent on hormonal stimuli. Paradoxically, however, these lesions are found in women past the menopause, a state characterized by hypoplasia and atrophy of the genital epitheliums. In this series of 203 cases of adenomyosis, there are found 23 patients in the menopausal group, employing as criteria either amenorrhea for periods in excess of six months, or definite symptoms and signs of the menopausal state. In previously published series of cases, the presence or absence of the menopause is not indicated, but, by the arbitrary selection of age 50 as the onset of the menopause, one may obtain a crude estimate of the number of menopausal patients in such series, for purposes of comparison. This would seem to be an acceptable procedure, inasmuch as the number of cyclical patients over that age is commonly much fewer than the number of menopausal patients below that age. In Table III it will be noted that 10.6 per cent of the cases fall into the menopausal group, an incidence much higher than one might expect.

\*See reference 10 for a review of these theories.

*Estrogenic hormone studies:* Blood extraction and bio-assay<sup>9</sup> failed to demonstrate the presence of estrogens in the amounts found during the latter half of a menstrual cycle, the extract of 30 c.c. of whole blood failing to elicit a threshold response in castrate rats.



Fig. 1.—Section of the adenomyomatous area ( $\times 90$ ).

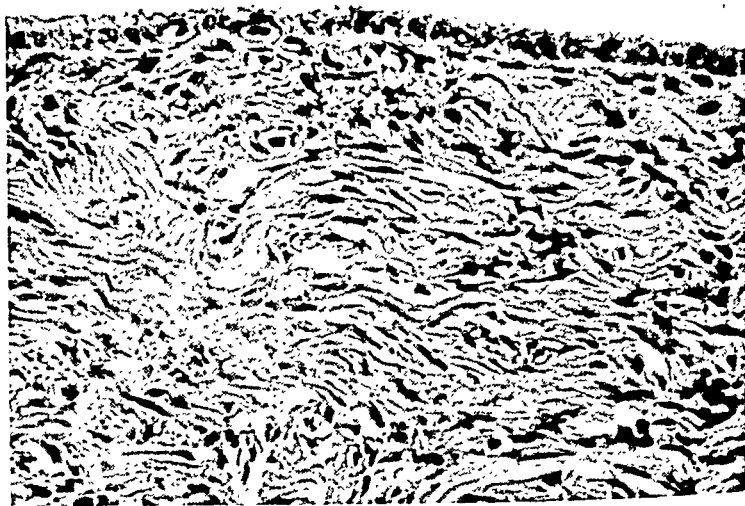


Fig. 2.—Section showing endometrium in a state of postmenopausal atrophy ( $\times 600$ ).

#### DISCUSSION

In the light of our previously outlined views of the pathophysiology of endometriosis, the sizable group of postmenopausal cases demands elucidation. Consistent with these views, the explanation suggests itself that the lesions found represent residua of tumors which had developed during the cyclical period, and thereafter have persisted in

We have recently encountered a patient classed in this group, and have been able to study the case clinically and endocrinologically.

#### CASE REPORT

B. V., a 63-year-old white woman, was admitted to Mount Sinai Hospital on Sept. 18, 1941, to the gynecologic service of Dr. S. H. Geist. She complained of aching right lower quadrant pain and backache present during the week prior to admission. Ten months previously she had visited a physician for a similar complaint and was told she had a right ovarian cyst. She remained symptom-free for seven months thereafter, when she had a sudden bout of vaginal bleeding lasting two days. Subsequently she was perfectly well until the present episode.

Menses had been entirely normal, without dysmenorrhea or excessive flow. Flow began at the age of 13, occurred every thirty days and lasted for three days. There were three pregnancies with two full-term deliveries. Last menstrual flow occurred in 1931 at age of 53, and during the following three-year period she had mild menopausal symptoms including hot flushes.

*Physical Examination.*—Patient was a small white female with graying hair, normal in distribution. Heart and lungs were negative. Breasts were atrophic. Thyroid was unenlarged. Pelvic examination: "Normal introitus. Cervix small, lacerated. Behind and somewhat to the right of the uterus is the lower pole of a soft, elastic, semicystic mass. The adnexa are not distinctly palpable."

*Laboratory Examination.*—Sedimentation rate was twenty-eight minutes (normally over 60 minutes). White blood count was 7300, and hemoglobin 71 per cent.

*Operation.*—The right broad ligament was occupied by a plum-sized cyst. This, together with the right tube and ovary, had undergone torsion, and displayed a hemorrhagic, infarcted appearance. The left adnexa were negative, the ovary appearing small, yellowish-white and atrophic. The uterus was slightly enlarged by the presence of a fundal adenomyoma and a small fibromyoma.

*Pathologic Study.*—Examination revealed an infarcted papillary parovarian cyst, with infarcted tube and ovary, on the right side. The left ovary showed atrophy; no active follicles or follicular cysts were present. Fat stain failed to demonstrate lutein tissue. The uterus contained an area of adenomyosis (Fig. 1) and a small fibromyoma. The endometrium consisted of a single layer of cells with no evidence of convolution or glandular activity (Fig. 2). Glycogen stain failed to reveal significant amounts of glycogen.

#### *Endocrinologic Study.*—

*Vaginal smear:* The individual cells were, on the average, smaller than those seen in smears from cyclical women.

*Vaginal biopsy:* There was moderate layering but no cornification. In some areas the thickness approached that seen in cyclical women, but for the most part the appearance was that of involutional hypoplasia.

*Gonadotropic hormone studies:* Urine extraction and bio-assay for gonadotropin<sup>s</sup> revealed a titer of at least 4 rat units per day, which is in the postmenopausal range. The ovarian responses were of the character associated with castrate gonadotropin.



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## SEXUAL LIBIDO IN THE FEMALE\*

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“The sour, shallow, sexless shrew is an imposter as  
a wife and her marriage is a fraud.”—Jordan.

MANY of the neuroses and ills of womenfolk may be traced to unhappy or unsatisfactory sexual relations. The wife without sexual desire, unless she has histrionic ability or other charms, frequently finds her marital relations strained. So frequently the complaint of frigidity is dismissed by the physician as unworthy of consideration or as a condition about which nothing can be done. Frigidity may be absolute; it may be relative. When frigidity is relative, desire is present but coitus does not culminate in complete gratification. Frigidity may be due to psychogenic or anatomic factors with resultant dyspareunia or vaginismus. The need for a better understanding of this problem cannot be questioned. The medical complexities and the social implications are many. The successful treatment of frigidity may circumvent the disintegration of a marital union or prevent a man's search of extra-marital adventure with its dangerous consequences. The literature is almost void of contributions to the subject.

Libido is a highly complex function in which psychologic, anatomic, neurologic, sentimental and hormonal components play important roles. The role of the hormonal component has not received due attention. The experiences gained by our group in evaluating the effects of pellets of testosterone propionate implanted in over 55 women and pellets of pure crystalline progesterone implanted in 16 women lead us to believe that love, libido, and marital harmony are frequently closely associated. At

\*Read by the senior author at a meeting of the Talladega County Medical Society, Talladega, Alabama, December 16, 1941.

relative quiescence and regression. It may indeed be that extragonadal, possibly adrenal, sources of estrogenic steroids supply a stimulus permitting continued, decelerated growth. The occasional finding of vaginal mucosa without regressive change<sup>11</sup> and the extraction of significant amounts of estrogenic substance from the urine of some women past the menopause<sup>6</sup> or after castration<sup>7</sup> would indicate that the menopausal state is not invariably one of complete estrin deprivation. It may further be reasoned that androgens, which are excreted in increased amounts with the advent of the climacteric,<sup>12</sup> may possess some estrogenic potency in the human being, although very little in the rodent. In this connection the demonstration of the estrogenic activity of desoxycorticosterone<sup>16</sup> is of interest. In general, however, it is true that estrogens are in very low titer in most menopausal women, and play a questionable role in the metabolism of these tumors.

On clinical grounds, the growth activity of the lesions appears to be in abeyance. In none of the 23 cases here cited were there symptoms attributable to the adenomyoma itself; in all cases operation was performed to relieve symptoms due to other pathology (fibroids, prolapsus, etc.). Certainly there is no evidence, either in our studies or in the literature, to indicate that these tumors can originate *de novo* after the climacteric, or even persist in active, symptom-producing growth.

In summation, the present investigation would indicate that, although uterine endometriosis is not infrequently present in the postmenopausal woman, such lesions are to be regarded as in a state of regression and atrophy, incapable of renewed growth activity. The tumors do not produce symptoms, except, conceivably, as a function of position or size attained during the premenopausal period of development.

#### SUMMARY

1. Theories of the origin of endometriosis are reviewed and the pathophysiologic role of estrogen stimulation is discussed.

2. A series of 203 cases of adenomyosis is presented, of which 23 were in women past the climacteric. An additional case is studied and reported.

3. The origin and fate of such tumors in the postmenopausal woman are discussed.

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thirteen months. In spite of the virilization of the patient, there was no loss of libido. In July, 1940, one of us<sup>7</sup> (R. B. G.) reported that the administration of 10 to 50 mg. of testosterone propionate in divided doses during the latter half of the cycle was sufficient to bring about an abatement of premenstrual tension. This adjustment probably relieves the nymphomaniacal tendencies of some women at this time.

Silberman and his colleagues<sup>8</sup> observed no effects upon libido in a group of menopausal patients treated by testosterone propionate. Salmon<sup>9</sup> noted that many of his patients experienced definite increase in libido during the course of injections and for several weeks thereafter. In many of these patients he found the clitoris erythematous and very sensitive to touch. The majority of these cases received more than 500 mg. of pure crystalline androgenic substance in one month. Recently, we have been able to confirm the impression of J. R. Groome<sup>10</sup> that frigidity may be due to a local defect of the clitoris which may be benefited by local application of testosterone propionate ointment. In a previous communication we reported that the subfascial implantation of testosterone propionate pellets in dosages varying from 25 to 145 mg. in a group of 10 patients was attended by a definite increase in sexual libido in every patient of the series.<sup>11</sup>

The increase in libido in the female following the administration of chemically pure androgenic substance in one form or another must be the result of a specific pharmacologic effect. The action may be mediated through minor changes in electrolyte balance or the effect may be directly on specific organs. Hartman<sup>12</sup> noted that testosterone invariably had an estrogenic action on the sex skin of the female monkey. The sex skin was always brilliant red. In this respect he found progesterone antagonistic to estrin. Testosterone did not antagonize the action of estrogens. Even in pregnancy, Hartman was able to blanch the sex skin with a sufficiently high dosage of progesterone. However, the concurrently injected estrogens and testosterone or both were sufficient to override the blanching action of the progesterone. In a series of 16 patients, progesterone pellets were implanted for various gynecic disorders. We were impressed with the fact that there was a decided depression in the sexual libido of several in whom it had been markedly exaggerated. One such case is described:

W. F., 23 years of age, unmarried, was referred to the endocrine clinic from the psychiatric clinic of the University Hospital. Her complaints were dysmenorrhea, nervousness, fainting spells, morbid restlessness and exaggerated sexual impulses. A pellet of 150 mg. of progesterone was implanted subfascially. Soon after there followed a decrease in her nervous tension state, a reduction in fainting spells from two to three per week to one in four or five weeks, amelioration of the dysmenorrhea and above all so marked a reduction in sexual desire that she no longer had any desire to "run around." She became fonder of her home and wished to do her share of the family chores. With the diminution in her libido, the haze seemed to clear; she saw the evil of her ways and was now repentant.

times, it appears, libido is merely a phenomenon depending on well-defined chemical substances.

In certain animals, the female of the species will receive the male in coitus only when in heat or estrus, and this is timed with follicle maturation. The period of heat in the dog lasts for a little longer than one week and occurs at six-month intervals. The cycle of the female chimpanzee simulates that of the human female. Unlike the latter, however, the chimpanzee will accept the male only during the height of genital turgescence, which corresponds to the phase of follicle maturity. During the luteal phase regressive changes set in, at which time she will fight off the male. It may be said then, as far as libido is concerned, that the corpus luteum hormone is opposite in its action to estrogens. This fact receives further corroboration in the work of Gillman<sup>1</sup> who has shown that the perineum of the baboon is a sensitive indicator in experiments involving the use of female sex hormones. Deturgescence in the normal adult female baboon is a positive phenomenon, due to the presence of progesterone and not to the absence of estrogens. Progesterone administered in total doses of 10 mg. or less will cause depression of the turgescence of the perineum.

The human female is unlike the dog or the chimpanzee. In fact, certain females exhibit marked nymphomaniacal tendencies during the week before the onset of menses. These same individuals frequently exhibit marked evidence of premenstrual tension.<sup>2</sup> Endometrial biopsies often reveal imperfect progestinal types of endometriums and blood estrogen titers may be somewhat higher than normal. It may be that in these cases excessive estrogen overrides corpus luteum activity. A high kidney threshold for estrogen excretion may be the prime fault. Following the administration of parenteral progestins to these patients in doses of 1 to 5 mg. every three to seven days or oral progesterone in 5 mg. doses during the last half of the menstrual cycle, there is frequently noted a detumescence of the sexual urge.<sup>3</sup>

Although estrogens have been administered with resultant increase in libido, nevertheless many women without sexual desire do not seem to respond to massive doses. Frequently, when estrogens fail, positive results have been obtained with testosterone propionate. Seventy-five to 200 mg. injected parenterally has frequently proved aphrodisiacal. This point is at variance with other investigators.

Rubenstein and his associates<sup>4</sup> have recommended testosterone propionate for the treatment of morbid sex cravings. They used 25 mg. at varying intervals for the relief of exaggerated sex urge. All the patients in their series had marked premenstrual tension. Abarbanel<sup>5</sup> also believes that nymphomania may be relieved with testosterone propionate. Some hold the opinion that androgens neutralize the action of estrogens, hence its value in the therapy of nymphomania. Testosterone propionate does not depress libido in the female. Wilson<sup>6</sup> in treating a young woman used a total dosage of 4,800 mg. of testosterone propionate over

## CASE REPORTS

The following brief case reports are selected to illustrate the points in question:

CASE 1.—C. F., aged 41 years, had menorrhagia and massive fibromyoma. Once had normal libido but had lost it. A pellet of 25 mg. of testosterone propionate was implanted twenty months ago. Her libido improved remarkably and has remained good to the present time.

CASE 2.—W. F., aged 30 years, married six years, complained of dysmenorrhea and dyspareunia. She never had any libido. In the four months since implantation of two 200 mg. pellets of testosterone propionate she has experienced marked increase in sexual satisfaction and feels much more in love with her husband.

CASE 3.—C. F., aged 25 years, with menorrhagia and fibromyoma, had three pellets, totaling 145 mg. of testosterone propionate, implanted subfascially. Before this procedure her libido was mild and she had sexual intercourse with her husband once or twice per week. Two months after implantation she volunteered the information that she had sexual relations once or twice per night. Her libido has remained very good throughout the fifteen months of her observation period.

CASE 4.—W. F., 40 years of age, complained of menorrhagia. Three pellets of testosterone propionate, totaling 146 mg., were implanted one year ago. Before implantation her libido was good. After this procedure it became excessive, but at the end of six months the libido returned to its pre-implantation status.

CASE 5.—W. F., 42 years of age, married 26 years, para ii, gravida iii. Her menstrual history was inconsequential except that she had had almost continuous flooding for three months. She also had urinary frequency, dysuria, hot flushes, and had lost 25 pounds in weight with her bleeding spell. Routine medication failed to arrest the menorrhagia. Two pellets, totaling 205.2 mg. of testosterone propionate, were implanted subfascially. Suction curettage before implantation revealed a hyper-estrogenic endometrium. Study of the vaginal secretions revealed the presence of trichomonads. Libido before implantation was poor. Bleeding stopped five days after implantation. Two weeks later an improvement in her libido was noted. One month after implantation the patient found that her libido was much better and her sense of well being had improved. Her menstrual periods became regulated, and the disturbances of micturition were alleviated. At the end of six months, when asked about her sexual nature, she answered "it was better than it had ever been in her life and that she and her husband were more in love with each other." Her weight increased 12 pounds, she was sleeping better, and had no hot flushes. Several weeks later she noted a sudden diminution in her libido. She regretted this very much for her home life and relations with her husband had improved so much. She hesitated to relate these facts for she said "It was not good talk for a church woman." Fortunately this was only a temporary depression of libido for it soon returned and eight months after pellet implantation still remains at a good level.

EVALUATION OF EFFECTS OF ANDROGEN PELLETS IMPLANTED IN  
55 WOMEN

One to four pellets of testosterone propionate weighing 25 to 200 mg. each were implanted subfascially in dosages from 25 to 400 mg. Statistics are available on 55 women between 22 and 53 years of age from whom information was obtainable as to their sexual urges before and after implantation. The patients have been followed from four to twenty-four months. Arrhenomimetic phenomena did not develop in any of these patients. Loeser obtained marked increase of libido in the patients in whom he implanted pellets of testosterone propionate, but his dosage was excessive, 600 to 1,500 mg., and he obtained signs of masculinization. We found that a 100 mg. pellet was the ideal dosage.

It seems impossible to increase libido in some psychologically frigid women who never have experienced sexual desire. On the other hand, restoration of the libido easily occurred following implantation in those women who at some time have known libido. Many married women volunteered the information that their loss of sexual desire led to marital discord. Following pellet implantation there was a return of coital pleasure which often terminated in orgasm. A re-awakened interest on the part of the husband usually followed, and husband and wife once more fell in love. The following phrase, trite and common, found frequent expression, "My husband treats me kindlier, is more attentive now and stays home evenings." In those women who had a marked to moderate degree of sexual desire before implantation all noted either no significant change or further increase in sexual pleasures. In two women with normal libido, there was a temporary decrease in sexual desire for several weeks immediately after pellet implantation, then there was a resurgence of the libido to a greater degree than that before the implantation. In several it was noted that the libido returned to the pre-implantation status by the end of the third to eighth month. In the majority, however, it persisted long after the pellets had been absorbed. Table I indicates that following implantation of testosterone propionate pellets there was an increase in sexual libido in most cases, while a resurgence of libido could be expected in almost every one of those who once had libido but had lost it.

TABLE I

|         | NO. | DEGREE OF LIBIDO BEFORE PELLETT | AFTER PELLETT     |                 |                    |           |          |
|---------|-----|---------------------------------|-------------------|-----------------|--------------------|-----------|----------|
|         |     |                                 | MODERATE INCREASE | MARKED INCREASE | TEMPORARY INCREASE | NO CHANGE | DECREASE |
| Group 1 | 7   | Very little or never had libido | 1                 | 4               | 1                  | 3         |          |
| Group 2 | 23  | Once had libido but lost it     | 8                 | 13              | 1                  |           |          |
| Group 3 | 14  | Mild to moderate libido         | 2                 | 6               |                    | 6         |          |
| Group 4 | 10  | Good to excessive libido        |                   |                 | 1                  | 8         | 1*       |

\*Nymphomaniacal reduced to normal.

## SCOPOLAMINE IN OBSTETRICS

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MUCH has been written concerning analgesia in labor and many diversified opinions regarding its merits have arisen. In view of these controversies, a report based upon the study of a single drug, namely, scopolamine, should be of value in considering the comparative effectiveness of the barbiturates and hypnotics in obstetrics.

Objections to the use of scopolamine have been made on the grounds that it is dangerous, because it lengthens the labor period and increases susceptibility to post-partum hemorrhage, that its action is uncertain, that there is great individual variation (the same dosage affecting patients differently), that it is responsible for a high percentage of operative deliveries, that it causes fetal asphyxia or cerebral damage, and that it is not applicable in private practice.

The successful results on 2,200 cases, reported by Dr. Bertha van Hoosen in 1928, did much to popularize this method of analgesia in labor. A similar technique has been employed in our cases, and the gratifying results obtained indicate the efficacy and safety with which this drug may be used in obstetric practice.

### TECHNIQUE OF ADMINISTRATION

The data presented here summarize the effects upon 1,481 private patients, 739 primiparas and 742 multiparas, personally attended by me at the Woman's Hospital of Detroit from 1930 to 1941.

1. *The Skin Test for Sensitivity.*—This is usually done sometimes during the last month of pregnancy. Scopolamine ( $\frac{1}{4},000$  gr.) is injected intradermally on the forearm. The reaction is observed within twenty minutes and is graded on the basis of the degree of redness surrounding the site of injection. If the diameter of the red area is 1 cm., the reaction is labeled 1-plus, etc. A definite correlation between the reaction and sensitivity to the drug exists. The degree of excitement during labor under scopolamine is usually proportional to the amount of skin reaction. It is certain that a patient who exhibits a 4-plus reaction will prove to be hyperexcitable during labor. However, such a reaction need not be regarded as a contraindication to the use of the drug, but rather as a warning that the patient may require a greater amount of attention during labor than would otherwise be necessary.

2. *Time of Administration.*—The drug is injected subcutaneously to permit of slow action, when the pains are recurring at regular intervals (every ten minutes), when uterine contractions are strong, of

## CONCLUSIONS

It must be admitted that sentimental, psychologic, and anatomical factors greatly influence the libido, nevertheless the role of the hormones is such that libido may be spoken of as a test tube chemical equation. Progesterone, the hormone of the corpus luteum in chemically pure crystalline state may be administered to depress excessive libido when present; on the other hand, chemically pure androgenic substances when properly administered decidedly increase the well being of the patients as well as the libido. Although the parenteral and oral administration of compounds of testosterone was frequently followed by increase in sexual urge, it was found that more consistent results could be obtained by pellet implantation. One hundred milligram dosage proved ideal. Pellets of testosterone propionate implanted subfascially are capable of providing a continuous prolonged nearly natural physiologic action. No fear of virilization need be entertained with this method and in dosages up to 400 mg. In almost every patient who once had known libido, a resurgence followed testosterone propionate pellet implantation.

These facts may provide a working basis for treatment. The psychotic tendencies of the nymphomaniac, the neuroses and unhappiness of the frigid female, and the problems of the incompatible couple, with their sociologic implications, are amenable to hormone therapy. There is much that can be done for the individual whose life may be colored by sexual frustration or sexual excess. The potentialities for correcting such maladjustments and for bettering human relationships may lie in the physician's hands.

The pellets of testosterone propionate are a product of Ciba Pharmaceutical Products, Inc. The pellets of pure crystalline progesterone are a product of Schering Corporation.

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3. *Respiration*.—Clinical doses of scopolamine stimulates respiration slightly, producing a more shallow, regular breathing. No appreciable change was observed in either direction.

4. *Blood Pressure*.—Examination after delivery showed no variation from the rate of pressure taken upon admission to the hospital. Only a few cases showed a slight tendency toward an increase in pressure.

5. *Temperature*.—A tendency for the temperature to show a slight increase was observed.

6. *Diminished Salivary Secretions*.—Thirst, dryness of the mouth and throat, and occasional enlargement of the uvula have been observed. The uvula may swell to five or six times its normal size, and may appear markedly reddened. The redness may persist for several days. Argyrol swabs or throat irrigations will correct this condition.

7. *Visual Disturbances*.—Blurred vision or faulty accommodation commonly occurs, but usually disappears from twelve to twenty-four hours later.

8. *Vomiting*.—This is not an especial characteristic of scopolamine anesthesia. Patients in labor may vomit without anesthesia of any kind.

9. *Retention of Urine*.—This condition occurs, but not specifically as a result of this drug.

10. *Excitement*.—Generally, excitement is reduced and the patient is tranquil and drowsy. However, on rare occasions, the patient may become extremely excitable, as we have previously mentioned, so as to require the vigilance of competent attendants. Of 1,301 recorded cases, there were 13 (1 per cent) of extreme excitement during and after medication, 4 of moderate excitement, and 7 of slight excitement. The number of excitable patients is not sufficient to present a very grave problem.

11. *Amnesia*.—Complete amnesia was obtained in nearly every case. (In a few instances, the memory of pain was very hazy or practically negligible.) The scopolamine narcosis was in each case adequate to cover the delivery period. The patients were unconscious of their surroundings, but the voluntary muscles necessary in the delivery were not inhibited in any way by the anesthetic.

#### CARE OF THE PARTURIENT

It is not necessary for the physician to be present at the bedside throughout the entire period of labor, provided he has an able staff of co-workers who keep him constantly informed regarding the progress of the labor. The attendants, however, must be alert. They must adhere strictly to directions as to amount and time of administration of the anesthetic. In warm weather, the patient's pulse and temperature must be taken every two hours, and the fetal heart sounds must be recorded before each dose. Bladder distention and inability to void must be watched, and catheterization performed when necessary. And finally, constant and careful watching is required to prevent the restlessness of an excited patient. Extremely excitable patients require special attention. Among the few instances of extreme excitement previously mentioned, there was one case of injury, the fracture of a metatarsal. Placing the patient in a crib with padded sides and giving a small amount of drop ether help to attain a more tranquil state in the very excited patient.

good character and frequency (lasting forty-five seconds), and when the cervix is effaced and dilatation has begun.

3. *Dosage*.—Because scopolamine is eliminated from the body in two hours and because of some occasional individual variation in the effectiveness of the drug, a moderate dosage has been standardized by van Hoosen. This dosage may be used judiciously in all normal deliveries. Three  $\frac{1}{100}$  gr. doses are administered within one hour (e.g., 1, 1:30, and 2:00), and the drug is effective to the point that the patient becomes unconscious of her surroundings. To maintain narcosis indefinitely, the same amount ( $\frac{1}{100}$  gr.) is repeated every two hours, counting from the time the third dose was injected. Repeated injections at two-hour intervals eliminate the necessity of various criteria for guidance in regulating the dosage, such as, pupillary dilation, memory tests, ataxia, or the reappearance of pain. Before each injection, however, a check should be made on the pulse and temperature of the mother, and the heart tones of the fetus.

Variations and individual differences establish a personal equation in the number of doses required. In our series of 1,481 cases, the injections ranged from 1 to 26, the latter without harmful effects or damage of any kind.

#### DOSES OF SCOPOLAMINE

TABLE I. NUMBER OF DOSES OF SCOPOLAMINE

| DOSES     | 3 OR LESS | 4-6 | 7-9 | 10-12 | 13-15 | 16-18 | 19-21 | 22 | 26 |
|-----------|-----------|-----|-----|-------|-------|-------|-------|----|----|
| Primipara | 192       | 295 | 97  | 44    | 12    | 4     | 1     | 2  | 1  |
| Multipara | 394       | 195 | 42  | 7     | 2     | 2     | 1     |    |    |

The average dosage was five. In the primiparas, the smallest number of doses was 3, the largest 26. In the multiparas, the smallest number was 1, the largest 21, and the average was 3.

In most cases reported here, ether was administered as a routine, although I personally consider the gases to be more satisfactory. With gas, the oxygen can be controlled better in the mixture. Such anesthetics as ethylene,  $\text{NO}_2$ , cyclopropane, in the order named, given with helium mixture, by skilled anesthetists, will improve the condition of babies at birth. In using ether, the mask should be removed from the patient's face just as soon as the child's brow appears over the perineum.

#### REACTION TO THE DRUG

The action of scopolamine does not become manifest until about one-half hour after the second injection. Therefore, no reaction is usually observed until after the administration of the third dose. Maximum narcosis is produced in one and one-half hours, the effects being:

1. *Sedation*.—The patient is generally tranquil. The head feels heavy, the face is flushed, the pulse and fetal tones are more rapid, and breathing is regular.

2. *Pulse*.—The pulse rate showed a slight increase one hour after the first injection. This is to be expected because of the possible vasomotor stimulation. This increase is followed by a decrease one hour before delivery, and a leveling off or an approach to normalcy one hour after delivery. No serious variation in the pulse rate is seen.

consisted of 2 toxemias, 2 prolapsed cords, 2 suppurative endometritis, 2 pyelocystitis, 1 pyelitis, 1 bronchopneumonia, 3 first-degree lacerations, 1 second-degree laceration, and 9 post-partum hemorrhages.

#### EFFECT UPON THE BABY

That the infant must pay the price for the mother's comfort and that the condition in which the infant is found at birth depends upon the type and amount of anesthesia absorbed by the mother is a fallacy which may have originated in the fact that the danger to the child, heretofore, was due to the simultaneous use of several drugs in obstetric analgesia. An anesthetic effect upon the infant may thus be produced. The drugs used may not have been antagonistic in their action on the respiratory center, but rather cumulative in effect. Thus, the result was usually one of fetal toxicity and fetal asphyxia. With the use of scopolamine alone, we have seen no ill effects upon the newborn infant.

TABLE V. INFANT BREATHING

|          | CASES | SPONTANEOUS<br>BREATHING | NO SPON-<br>TANEOUS<br>BREATHING | REQUIRED<br>RESUSCITA-<br>TION | STILL-<br>BIRTHS | DIED |
|----------|-------|--------------------------|----------------------------------|--------------------------------|------------------|------|
| Number   | 1,276 | 1,104                    | 96                               | 75                             | 8                | 2    |
| Per cent |       | 86.52                    | 7.52                             | 5.87                           | 0.62             | 0.15 |

*Condition at Birth.*—a. *Appearance:* The baby is usually pink following delivery under scopolamine anesthesia. The congestion of the surface vessels diminishes the blood supply in the deeper brain structure and this markedly reduces the possibility of rupture of the vessels in the region of the brain. It appears that cerebral injuries are less likely to occur.

b. *Fetal Heart Sounds:* When the fetal heart sounds were heard, the babies, in all cases, were born alive, usually breathing spontaneously.

c. *Oligopnea:* This somnolence is a brief delay in breathing which is occasionally encountered. It is transient and need cause no alarm. The child will promptly and readily respond to stimulation, and keeping it warm is essential for prompt recovery.

d. *Cyanosis:* If supplemental anesthesia is carefully administered, and the baby is well oxygenated as it is delivered, there will be no cyanosis.

e. *Fetal Toxicity:* We have not observed any case of fetal toxicity in this series.

f. *Fetal Asphyxia:* Scopolamine properly administered does not cause this condition, but faulty or improper technique might do so.

g. *Stillbirths:* Of 8 stillbirths, 4 were doubtful with regard to fetal heart sounds prior to injection, and there is no reason to ascribe the others to the anesthetic used.

h. *Resuscitation:* Before we used scopolamine alone, we had used the combination of scopolamine and morphine, supplemented by ether. In one month, it was observed that of 40 babies delivered, 15 required resuscitation. With scopolamine alone, a comparison with 40 babies was made the following month, at which time only 4 required resuscitation. The agents most frequently used for this purpose were: tracheal catheter, coramine, alphalobeline, metrazol injection, caffeine or adrenalin, and oxygen from a tank tube and funnel.

## RESULTS BASED UPON STATISTICS

TABLE II. NUMBER OF HOURS OF LABOR

| Hours     | 1-5 | 6-10 | 11-15 | 16-20 | 21-25 | 26-30 | 31-35 | 36-40 | 41-45 | 46-50 | 61 | 72 | 90 |
|-----------|-----|------|-------|-------|-------|-------|-------|-------|-------|-------|----|----|----|
| Primipara | 56  | 179  | 178   | 95    | 61    | 27    | 11    | 9     | 6     | 2     |    | 1  | 1  |
| Multipara | 80  | 244  | 115   | 42    | 22    | 4     | 6     | 6     |       |       | 1  |    |    |

1. *Length of Labor.*—Of 1,301 recorded cases, in which the length of labor was carefully timed, 655 were primiparous and 646 multiparous. The shortest primiparous labor was two hours, the longest ninety hours, and the median, twelve hours. The shortest multiparous labor was two hours, the longest, sixty-one hours, and the median six and one-half hours.

2. *Loss of Blood.*—Uterine bleeding was never excessive with scopolamine anesthesia, except in rare cases where gynoplastic repair of old lacerations followed. In fact, the tendency to hemorrhage is less than with any other drug which we have used.

3. *Post-partum Course.*—Scopolamine has no ill effect whatever upon the puerperium. With the possible exception of an occasional complication arising from subsequent surgical involvement, the convalescence period of these patients was smooth and rapid. Of 1,300 recorded cases, there were only 9 post-partum hemorrhages (0.7 per cent). Because of the absence of shock or exhaustion, the patients seem to make quicker recovery than those who have been delivered without this drug. Despite the drying effect and limitation on the mucous secretions during labor under scopolamine influence, lactation does not seem to be affected.

TABLE III. VARIOUS TYPES OF DELIVERY

|                | RECORDED<br>CASES | NOR-<br>MAL | LOW<br>FOR-<br>CEPS | MID-<br>FOR-<br>CEPS | HIGH<br>FOR-<br>CEPS | BREECH<br>EX-<br>TRACT | PODALIC<br>VERSION | CESA-<br>REAN<br>SECTION | MOR-<br>TALITY |
|----------------|-------------------|-------------|---------------------|----------------------|----------------------|------------------------|--------------------|--------------------------|----------------|
| Primiparas     | 654               | 284         | 266                 | 17                   | 1                    | 26                     | 45                 | 13                       | 2              |
| Multiparas     | 639               | 451         | 88                  | 9                    | 0                    | 19                     | 55                 | 5                        |                |
| Total per cent |                   | 56.76       | 27.38               | 2.01                 | 0.07                 | 3.47                   | 7.73               | 1.46                     | 0.15           |

4. *Types of Delivery.*—No tendency toward any one type of delivery as a result of scopolamine anesthesia was observed. Low forceps were often used routinely.

TABLE IV. TYPE OF SURGERY

|          | RECORDED<br>CASES | EPISIOTOMY<br>(ROUTINE) | PERINEOR-<br>RHAPHY | AMPUTATION<br>OF CERVIX<br>(LOW) | NO SURGERY |
|----------|-------------------|-------------------------|---------------------|----------------------------------|------------|
| Number   | 1,300             | 1,059                   | 80                  | 3                                | 137        |
| Per cent |                   | 81.39                   | 6.14                | 0.23                             | 10.53      |

5. *Surgery.*—In making comparisons with other anesthetics, statistics show that scopolamine does not increase the incidence of operative intervention.

6. *Complications.*—No complications were ascribable to scopolamine narcosis. Among 739 primiparas, complications occurred in only 1.9 per cent; while in 742 multiparas, there were only 1.7 per cent. These

prostration were reported on that day in the city. The patient's temperature was 99° F. She was given  $\frac{1}{100}$  gr. of scopolamine twice. Before the third dose, her face became flushed, green amniotic fluid escaped from the vagina, dilatation was 2 cm., and the fetal heart tones were irregular (180) and distant. Immediate low section was done under nitrous oxide ether anesthesia. The baby was resuscitated with tracheal catheter, its temperature being 102° F. The mother's temperature continued to rise every hour for five hours. At that time, the axillary temperature was 107° F., pulse 160, and respiration 42. An hour later a twitching of the facial muscles was seen. Consultation confirmed the diagnosis of heat stroke, and twenty-six hours after the section the patient died.

Several other patients admitted to the hospital within the next two days of the heat wave showed an elevation of temperature up to 105° F.

The only other maternal death in our records occurred on Aug. 25, 1932, when the temperature was 91° F., the barometric pressure 30.32. This patient, a 33-year-old primipara, had a spontaneous face delivery of a 6-pound 2-ounce baby after a twelve-hour labor, under 8 doses of scopolamine. Her temperature on admission was 98.2° F., and no temperatures were taken during labor. The baby's temperature at birth was 100° F. The patient went into collapse one-half hour after delivery and died three hours later. While death in this case may have had some relation to the high temperature, it may also have been due to cardiac dilation.

#### COMPARISON WITH OTHER ANALGESICS

Obstetric anesthesia has undergone considerable metamorphosis. Twenty years or so ago, the common practice of administering nitrous oxide at the patient's bedside at each labor pain proved costly for the patient, worked hardships on the department of anesthesia, and the results obtained were only mediocre. With the introduction of intravenous anesthesia, the problem of short labor could be handled with greater facility but, when labor was prolonged over two or three hours, the results were unsatisfactory.

Gwathmey's anesthesia was a great advance, but it also had its disadvantages. The maximum effect lasted three or four hours. Then, it had to be repeated. One could never be certain as to the dosage the patient was getting or retaining. However, favorable results could be obtained in home labors, and therein does its merit lie, for it is still a good method for home deliveries. Evipal by rectum, suggested by Gwathmey, is subject to the same criticism as the original Gwathmey formula.

My personal experience with the various anesthetics has led me to believe that combinations, such as morphine-pantopon, or dilaudid-scopolamine, produce sleepy babies which usually require resuscitation; while nembutal-scopolamine, or any of the barbiturates, seems to produce a greater restlessness on the part of the mother, and the babies are often cyanotic.

Paraldehyde seems to prolong multiparous labors, during which time it is possible for the patient to become restless, sustain serious injury, and require forceps delivery to complete the labor.

i. *Fetal Mortality*: Our fetal mortality is extremely low, being 0.13 per cent. With controlled scopolamine narcosis, fetal deaths are definitely diminished and the few deaths which did occur had other very specific causes.

j. *Mental Development of the Child*: Cerebral injuries at birth cannot be attributed to scopolamine analgesia. Where injuries occur, a review of the case would undoubtedly reveal etiologic factors, such as rapid, violent labor, difficult forceps delivery, etc. The drug itself has no effect whatsoever upon the mentality or development of the infant. The children whom we have delivered under scopolamine several years ago, and whom we have followed up, are as well developed physically and alert mentally as any other group of normal children. These children have now reached the school age and although the psychometric studies which we are now making of the children have not as yet been completed, the results so far obtained reveal a very superior rating, due, of course, to their respective innate capacities. We can only report what we have observed, namely, that no mental impairment resulted from the use of scopolamine.

#### CONTRAINDICATIONS

1. *Physical Condition of the Patient*.—Certain conditions have been listed in which scopolamine is considered contraindicated, some of which, in our experience, we have not found justifiable. We feel that in such cases as weak fetal heart sounds, expected short labor, disproportion between the fetal head and the mother's pelvis, premature cases, or controlled Graves' disease, scopolamine produces no ill effects. Even in tuberculosis, if the patient has undergone a phrenic operation, or thoracoplasty, as long as there is no intense activity of the lesion, scopolamine may be used with comparative safety.

There are, however, some instances where the use of scopolamine is unwise for very obvious reasons: In acute respiratory disease, where the inhibitory action upon mucous secretions would produce a drying effect; in certain cardiac or circulatory diseases, such as coronary or acute decompensation (although cases of compensated mitral lesions seem to tolerate the drug rather well); in active eclamptic convulsions, it is better to keep the blood pressure depressed and avoid any possibility of excitement which the drug may produce; in active toxic goiter, the already too rapid pulse might be stimulated further; in acute or subacute nephritis, where the drug might have a cumulative effect, its elimination being threatened by impaired kidney function; in pulmonary edema, where no masking of symptoms of a disease so serious in nature, should occur; and in marked albuminuria, where the diminution of secretions by scopolamine would place an added burden upon the kidneys.

2. *Atmospheric Conditions*.—Extremely hot weather is not conducive to favorable scopolamine narcosis. Because of the tendency to raise the patient's temperature, the dosage should be reduced considerably, or omitted entirely. If this type of narcosis is desired when atmospheric temperature is above 90° F., the patient's temperature should be taken hourly. The only maternal deaths occurring in this entire series were during extremely hot weather.

One patient, Mrs. R., primipara, with justominor pelvis, entered the hospital in labor on July 10, 1936, the temperature in Detroit being 102° F. and barometric pressure 29.93. Ninety-one deaths from heat

10. Operative intervention is comparable to any normal curve of distribution in hospital practice.

11. We have seen no evidence of maternal or fetal toxicity or intolerance to the drug.

12. Scopolamine is not harmful to the newborn infant. Cyanosis, fetal asphyxia, or fetal mortality could not be ascribed to this drug.

We feel, therefore, that on the basis of the evidence presented, scopolamine used alone, judiciously, under standardized conditions, by experienced and competent attendants, is the best anesthetic, during labor, which the obstetrician can offer at the present time in hospital practice.

Thanks are extended to Stanley Axelrod, M. L. Axelrod, Lloyd Mallin, and Helen Esser Fenton for their aid in the compilation of the data.

1104 MACCABEE BUILDING

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## THE ELECTROENCEPHALOGRAM IN PREGNANCY\*

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THIS study was planned as a preliminary survey of the electroencephalogram in pregnancy with the special purpose of determining whether the electrical activity of the cortex is modified in normal pregnancy and whether there is a difference between the electrical activity of the cortex in normal pregnancy and in pregnancy complicated by toxemia.

### MATERIAL AND METHOD

The electroencephalograms of 28 pregnant women were obtained. Of these, 20 had normal pregnancies; 3 had mild pre-eclampsia; 4 had severe pre-eclampsia; 1 had eclampsia, and in 1 case the pregnancy was interrupted because of heart failure due to severe rheumatic heart disease. In 17 cases, an electroencephalogram was obtained after termination of pregnancy. Most of the records were taken in the last two weeks of pregnancy and in the first two weeks post partum.

The activity of both frontal, parietal, and occipital areas were recorded on paper with a Grass three-channel electroencephalograph. Unipolar leads were used with the indifferent electrode on the two ear lobes. At the same time, the activity of various cortical areas was recorded as a shadowgram on film, and analyzed into spectra with the Grass frequency analyzer.

### RESULTS

In all but 3 of the 16 cases where pre- and post-partum records were obtained, cortical activity was slower during than after pregnancy (Fig. 1). In 2 cases, it was unchanged, and in one, it was faster dur-

\*This study was aided by grants from the John and Mary R. Markle Foundation and the Rockefeller Foundation.

Pentobarbital causes undue restlessness and requires very close watching of the patient.

Spinal anesthesia, generally considered dangerous in obstetric practice, has been used occasionally in tuberculous cases by us and we can report very satisfactory results.

We have attempted the use of a combination of a local anesthetic with scopolamine until the baby is delivered, but have found difficulty in maintaining sterile drapes and keeping the patient quiet. It is almost impossible to put the patient in stirrups and to do an episiotomy without having her move her hips during the application of the forceps or the delivery of the child.

Recent scientific work on fetal respiration by Rosenfeld, Snyder and Dreisbach has shown scopolamine to be the only drug in the analgesic narcotic group used in obstetrics that does not depress intrauterine fetal respiration.

Cook County Hospital studies on obstetric anesthesia suggest an increased prothrombin time in babies when barbiturates are used.

#### SUMMARY AND CONCLUSIONS

1. There is no uncertainty regarding the action of scopolamine. Individual variations may be anticipated by the sensitivity test. This drug is rapid in action, constant when standardized dosage is used, and easy to administer.
2. With proper precautions, it is safe for both mother and child. Pulse, respiration, blood pressure, and temperature suffer no ill effects from the drug's action.
3. Amnesia is quite complete. The patient passes the ordeal of labor with a minimum of discomfort and wakes up after delivery well rested.
4. We have seen no alteration or interference with uterine contractions nor with the normal processes of labor under the drug's influence. The mother is not asked to cooperate with the physician or attendants. The contractions continue as they would normally in labor and the patient uses the expulsive forces automatically when the head is on the perineum.
5. The length of labor is not increased. Our data, on the contrary, shows a considerable decrease in this period under scopolamine narcosis.
6. The loss of blood is minimal and the drug is responsible for a lesser tendency to hemorrhage.
7. Convalescence after scopolamine anesthesia is rapid and smooth. The post-partum course is in no way hampered nor affected by its use.
8. Lactation follows in a normal manner. No influence seems to be exerted by the drug.
9. No complications were attributed to this drug. The two deaths which have been described were due to excessive heat and cardiac dilatation.



TABLE I

| CASE | PREPARTUM                       |                  | POST PARTUM                    |                       |                                |                       | CLINICAL<br>DIAGNOSIS |
|------|---------------------------------|------------------|--------------------------------|-----------------------|--------------------------------|-----------------------|-----------------------|
|      | DAYS<br>BEFORE<br>DELIV-<br>ERY | EEG              | DAYS<br>AFTER<br>DELIV-<br>ERY | EEG                   | DAYS<br>AFTER<br>DELIV-<br>ERY | EEG                   |                       |
| 1    | 2                               | 9½/sec.          | 7                              | 10/sec.               |                                |                       | Normal pregnancy      |
| 2    | 1                               | 11 /sec.         | 7                              | 12/sec.               |                                |                       | Normal pregnancy      |
| 3    | 1                               | 11½/sec.         | 3                              | 12/sec.               |                                |                       | Normal pregnancy      |
| 4    | 12                              | 10½/sec.         | 1                              | 11/sec.               |                                |                       | Normal pregnancy      |
| 5    | 10                              | Slow             | 1                              | 9/sec.                |                                |                       | Normal pregnancy      |
| 6    | 10                              | Slow             | 9                              | 11½/sec.              | 67                             | 11½/sec.              | Normal pregnancy      |
| 7    | 10                              | 9½/sec.          | 12                             | Low-V.*<br>fast       |                                |                       | Normal pregnancy      |
| 8    | 9                               | Slow             | 2                              | 9½/sec.               |                                |                       | Normal pregnancy      |
| 9    | 1                               | Slow             | 9                              | Very slow             |                                |                       | Normal pregnancy      |
| 10   | 4                               | Very slow        | 5                              | Slow                  | 55                             | Slow                  | Normal pregnancy      |
| 11   | 2                               | Slow             | 7                              | Slow                  |                                |                       | Normal pregnancy      |
| 12   | 1                               | Slow             | 10                             | Low-V.*<br>fast       |                                |                       | Normal pregnancy      |
| 13   | 5                               | 9 /sec.          | 4                              | 9½/sec.               | 60                             | 9½/sec.               | Mild pre-eclampsia    |
| 14   | 36                              | Slow             | 15                             | Low-V.*<br>fast       |                                |                       | Pre-eclampsia         |
| 15   | 1                               | High-V.*<br>fast | 20                             | High-V.*<br>very fast | 74                             | High-V.*<br>very fast | Pre-eclampsia         |
| 16   | 2                               | Slow             | 9                              | 8/sec.                |                                |                       | Pre-eclampsia         |
| 17   | 90                              | Very slow        | (Hys-<br>terec-<br>tomy)       | Slow                  |                                |                       | Rheumatic heart       |

\*Voltage.

TABLE II

|                                  | SLOW | NORMAL | HIGH-V. FAST |
|----------------------------------|------|--------|--------------|
| Control (100 nonpregnant women)  | 8%   | 85%    | 7%           |
| Normal pregnancy (20 cases)      | 40%  | 60%    | 0            |
| Pregnancy with toxemia (8 cases) | 40%  | 10%    | 50%          |

## DISCUSSION

Slow cortical activity and high-voltage fast activity are common in a variety of conditions associated with evidence of cerebral dysfunction.<sup>1</sup> All conditions in which the incidence of convulsions is higher than in the general population are associated with a high incidence of electroencephalograms that are classified as slow or high-voltage fast. Tonic-clonic convulsions are usually accompanied by an abnormal acceleration of cortical activity,<sup>2</sup> and grand mal seizures can be predicted in epileptics by an increase in the amount of fast activity.<sup>3, 4</sup> The occurrence of abnormally fast activity in half of the patients with pre-eclampsia suggests that in pre-eclampsia cortical activity is commonly in a subconvulsive state. Endocrine and metabolic factors are known to alter the electrical activity of the cortex,<sup>5-10</sup> but an increase in cortical frequency, such as occurs with an increase in metabolic rate, could not explain the present findings, nor would any known change in sugar metabolism. Detailed consideration of the factors that may be responsible for the

ing pregnancy. In 4 cases, a second post-partum record was obtained, two or more months after delivery; in all 4 cases, this record also was faster than the prepartum record. This suggests that the change occurring with pregnancy can be properly regarded as a slowing of cortical activity during and as a return to the patient's usual cortical frequency after delivery. Table II contains further evidence that the deviation is in the direction of slowing during pregnancy. From this table it may be seen that 40 per cent of the patients with normal pregnancy had electroencephalograms which were classified as slow, a much higher incidence of slow records than has been observed in any normal control series. The complete absence of high-voltage fast records in this group is also noteworthy.

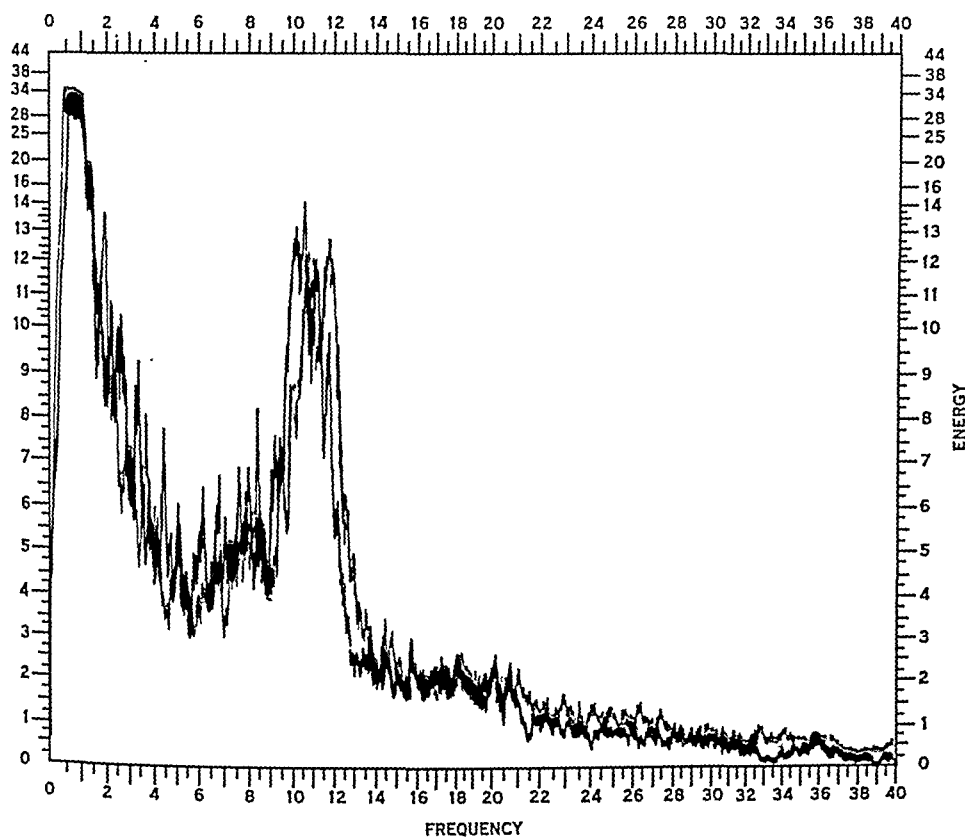


Fig. 1.—Typical shift in the cortical frequency spectrum to the slow side during pregnancy. *Black curve*, twelve days before term; *red curve*, one day post partum. Frequency is shown in cycles per second, and energy in arbitrary units that are convertible to millivolts. This is Case 4 in Table I. The spectra were made with a Grass analyzer from records of the electrical activity of the right occipital area.

Slow records occurred as commonly among patients with toxemias as among patients with a normal pregnancy (Table II). The difference between the two groups appears to lie in a greater incidence of high-voltage fast records among patients with toxemia and in a smaller incidence of perfectly normal records. In the one case of eclampsia that was studied, the record was obtained during stupor; the cortical activity at that time was extremely slow. In one case studied just before pregnancy was interrupted because of severe cardiac decompensation, the electroencephalogram was also slow.

attendant with no ill-effects. It is evident from the reports in the literature and the wide clinical use of the drug that toxic side-effects occur in a very small percentage of cases.

The posterior pituitary extract used in obstetrics is water soluble, purified to remove inert protein, and contains a pressor and oxytocic principle. Efforts have been made to separate the two, but it is generally accepted that any solution of one contains minute amounts of the other.<sup>5</sup> Three different varieties of toxic reactions following the use of pituitary have been noted. The first and most common is the reaction called pituitrin shock. It is characterized clinically by pallor, increased pulse rate and fall in blood pressure, headache with occasional abdominal pain, nausea and vomiting. These phenomena are caused by a generalized capillary vasoconstriction and the most alarming symptoms: pallor, rise in pulse rate and drop in blood pressure are due to coronary constriction with resultant anoxemia of the cardiac musculature, consequent vasodilatation and lessened cardiac output.<sup>6, 7</sup> A second type of pituitary reaction is one resembling true anaphylactic shock and is characterized by severe urticaria and a localized or general pruritus. Cases of patients have been reported with marked edema of the eyes, face, glottis, or lungs, with or without severe shock.<sup>8-10</sup> We have been unable to find what we believe to be a third type of toxic response, reported in American literature although cases have been reported from abroad. This third type is characterized by tetanic convulsions with either a rise or drop in blood pressure.

In 1915 Seifert<sup>11</sup> reported tinnitus, anxiety, albuminuria, unconsciousness, and convulsions following the use of posterior pituitary extract. In 1922 H. Vermelin<sup>12</sup> reports convulsions following the use of 1 c.c. of the extract in a previously normal primiparous parturient. In the same communication Van Cauwenberghe reported convulsions in a primipara seventeen hours after delivery, and Wegmeersch noted convulsions after the use of the drug. In 1927 Lawrence and Shackle<sup>13</sup> described convulsions in a multipara, occurring four days post partum just after the drug had been used for subinvolution. This case was complicated by a severe diabetes and brings to mind DeLee's<sup>15</sup> warning to be careful of the use of pituitary in diabetics and patients with thyroid dysfunction. In 1936 Schockaert,<sup>14</sup> of Brussels, published the same reaction in a primipara with a previously normal prenatal course.

A case of convulsions following the intravenous administration of 3 minims of pituitary extract is reported herewith.

Mrs. O., a 37-year-old primipara, was under prenatal supervision from June 14, 1941. There had been no serious illnesses and no operations. Her family history was significant in the light of subsequent events in that she had one sister who suffered from severe epileptic attacks. The catamenia had been normal and regular, and her last period began March 12, 1941, making her expected date of confinement Dec. 19, 1941. The general physical examination revealed no abnormalities, the blood pressure was 120/70, the examination of the urine disclosed no albumin

modification of cortical frequency in pregnancy will be deferred until more data are available.

### SUMMARY AND CONCLUSIONS

An electroencephalographic study of 28 pregnant women, 8 of whom had pregnancy toxemias, indicates that the electrical activity of the cortex is slowed in pregnancy and that, as a group, patients with pregnancy toxemias show more high-voltage fast activity and less normal activity than patients without toxemia.

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## CONVULSIONS FOLLOWING THE INTRAVENOUS ADMINISTRATION OF PITUITARY EXTRACT

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A THOROUGH survey of the literature concerning the use and abuse of posterior pituitary extract in obstetrics reveals that the vast majority of clinical and laboratory investigators condemn its indiscriminate use in the first stage of labor; sanction a judicious use in the second stage and generally laud its beneficent properties in the third stage. It is probably fair to assume that many obstetricians use pituitary extract without much consideration of the possible toxicology involved.

In 1933 the senior author<sup>1</sup> reported the intravenous use of the extract in 100 cases of cesarean section with uniformly good results and no toxic effects. In 1936 Pastore<sup>2</sup> reported on the use of the drug in the third stage of labor and in the control of post-partum hemorrhage, used intravenously, with one death due to shock. White,<sup>3</sup> in 1938, reported the intravenous use in 630 cases with no bad results. In 1940 Gardiner, Sprague, and Bradbury<sup>4</sup> found that the intravenous use of the drug was

a 10 per cent solution, and sodium luminal, 5 gr., was administered intramuscularly. A catheter was introduced to the bladder and nine ounces of urine obtained; this specimen showed a large trace of albumin. In a period of five hours a total of 9 ounces of urine was excreted. Magnesium sulfate therapy was continued with a 25 per cent glucose solution on alternate hours plus sodium luminal sedation. During this period of seventeen hours her urinary output was 26 ounces and each specimen showed a large trace of albumin. During the same interval her blood pressure varied from 190/110 to 170/100. She was very drowsy but when she did respond she complained only of occipital headache.

Seventeen hours after the first convulsion a second fit occurred and this also lasted for one minute. Following the second convulsion the patient lost control of her sphincters and was placed on constant drainage. A lumbar puncture was then performed. The initial pressure was 210; this was reduced to fifty by the slow withdrawal of 20 c.c. of spinal fluid over a period of ten minutes. Examination of the fluid revealed one lymphocyte and numerous red blood cells. The spinal tap was easily performed and was believed to be atraumatic.

During the course of the next six hours, continuing with magnesium sulfate and glucose on alternate hours, the pressure dropped gradually and varied between 158/170 and 190/100. Paraldehyde was substituted for sodium luminal because the patient was restless. A second spinal tap was performed at the end of this six-hour period, and the pressure was found to be 70. Examination of the eye grounds at this time revealed no evidence of increased intracranial pressure. All medication with the exception of paraldehyde was stopped. At this time the blood pressure was 140/90. The patient was controlled on gradually decreasing doses of paraldehyde and the blood pressure dropped, with short exacerbations, until on the third postoperative day it was 120/70. Albumin gradually disappeared from the urine and on the third day it was absent. The urinary output on the second day was 55 ounces and on the third day was 87 ounces. The occipital headache disappeared after the second lumbar puncture and did not recur. The surgical wound healed well; there was no postoperative nausea or vomiting and no distention. The patient was out of bed on the eleventh and discharged on the fourteenth day post partum.

#### DISCUSSION

The point will be raised that the convulsions were the result of a fulminating post-partum eclampsia. We believe this may be ruled out by a consideration of the patient's past history and prenatal course which was entirely negative; also by our personal observations of the onset of the syndrome which immediately coincided with the intravenous administration of the extract. She was seen one day before operation at which time she was symptom free, and the blood pressure and urinary findings were normal. On the morning of admission to the hospital the patient voided a large quantity of urine as noted in the nurse's report. In this specimen there was a slight trace of albumin, but her membranes had ruptured and the urine was contaminated with amniotic fluid. There was no edema at any stage and a speedy return to normal without residua was made.

or sugar, and the sediment was negative. Her weight was 114 pounds. There was no evidence of endocrine imbalance. Throughout her pregnancy the urine remained free of albumin and her blood pressure was within normal limits. She was last seen in the office on Dec. 26, 1941 and at that time her blood pressure was 122/78, the urine was negative, and she weighed 137 pounds, the baby was large and the vertex was riding high. Because she was overdue, x-ray studies were made of her pelvis. These confirmed the impression of cephalopelvic disproportion, and she was booked for cesarean section. Early the following day the patient was admitted to the hospital with a history of ruptured membranes, slight show, and irregular, mild uterine contractions. A voided specimen at this time showed a slight trace of albumin, and on the nurse's chart was recorded the fact that the patient passed a large amount of urine at the time, although it was not measured. Throughout the morning the patient continued having mild uterine contractions. No medication was given. Immediately before the operation she stated that she felt fine and had no complaints. Her blood pressure at this time was 120/70. She received no preoperative medication, and at 11:15 A.M. spinal anesthesia was administered. The spinal needle was placed in the third lumbar space and 75 mg. of novocain crystals were mixed with 2 c.c. of spinal fluid and injected slowly. A skin wheal had been previously raised with a mixture of 1 per cent novocain and 50 mg. of ephedrine sulfate. Just before and for some time after the administration of the anesthesia the blood pressure was recorded at 130/70, and there was no immediate change following the injection of the anesthesia. The patient was placed in moderate Trendelenburg position fifteen minutes after the administration of the anesthesia. The blood pressure remained at the above-mentioned level, and there was no subjective complaint from the patient until after the administration of three minims of obstetric pituitrin. This was given intravenously in 4 c.c. of saline solution immediately after the removal of the baby through a low transverse cervical incision.

Immediately after the pituitary extract was given the patient developed a sharp pain in the chest in the region of the xiphoid process. Simultaneously she complained of a sharp pain in the head which localized in the occipital region. Shortly thereafter she became nauseated and regurgitated. The nausea and the vomiting subsided with the administration of oxygen, but the chest pain and headache persisted. The patient was given 1 ampoule of ergometrine intramuscularly after the delivery of the placenta. She was also given morphine sulfate, grain  $\frac{1}{6}$ , because of her complaint of headache and substernal pain. There was no sharp rise in blood pressure readings, but there was a steady trend upward beginning with the administration of the solution of pituitary extract, at which time it was 130/70, until the operation was concluded twenty-five minutes later when the recorded blood pressure was 150/80. Throughout the entire operation the pulse varied between 92 and 96. The patient was returned to her bed from the operating room and in thirty minutes her pressure was recorded at 210/110. The nurse's chart states that she was complaining bitterly of occipital headache and was very alert. The patient was given 3 gr. of nembutal and became drowsy.

For the next three hours her pressure varied between 210/110 and 188/100, and during this time her pulse varied from 84 to 100. Three hours after the administration of the pituitary extract and the onset of her symptoms, the patient had a generalized tetanic convulsion which lasted for one minute. Intravenous magnesium sulfate, dose 20 c.c. of

reports an increase of posterior pituitary substance in the serum of an eclamptic patient. A number of workers, however, notably Byrom and Wilson<sup>26</sup> and more recently Dexter and Weiss<sup>19</sup> were unable to duplicate the results of the above workers. In consideration of the present case, the observation of Keith, Freidman and Barbour<sup>27</sup> is interesting. These men found that the presence of posterior pituitary extract in the cerebrospinal fluid stimulated the cerebral vasomotor centers, causing a prolonged rise in blood pressure. The cerebral arteries were constricted causing a cerebral anoxemia. This in turn favors increased capillary permeability with perivascular exudation, edema of the brain, and increased intracranial pressure.

Our patient's past history was negative for any sign of cerebral sensitivity, but there is a familial history of epilepsy and the question of cerebral dyskinesia might arise in seeking an explanation of her response. It is to be hoped that this presentation will stimulate the publication of any similar reactions which may have been observed. Since this unfortunate incident occurred, the authors have used an intravenous ergot preparation instead of pituitary extract.

#### SUMMARY

A case of post-partum convulsions in an apparently nontoxic parturient patient following the intravenous administration of three minims of pituitary extract is recorded.

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In 1895 Oliver and Schaefer<sup>16</sup> described a rise in blood pressure due to posterior pituitary extract and they ascribed this phenomena to a generalized vasoconstriction. They noted that this rise was particularly marked in the intravenous use of the substance. It is evident that individuals vary in their susceptibility and reaction to the drug. Moffat<sup>17</sup> studied the effect of pituitary extracts on the blood pressure in man and concluded that there was no constant rise but rather a tendency to drop after intramuscular use. In a few individuals there was a marked change but this was frequently a fall rather than a rise. In a study on the effects of posterior extract in pregnant women Dieckmann and Michels<sup>18</sup> noted that the magnitude of the vasomotor response did not bear a direct relationship to the size of the dose. This observation was confirmed by Dexter and Weiss<sup>19</sup> working on rabbits, who determined that the height of the peak rise in blood pressure and the duration of the same were not proportional to the dosage. Dieckmann and Michels, studying the effect on nonpregnant women, found a decrease in the volume of the urine with an increase in urinary chloride and little or no rise in blood pressure. In known pre-eclamptics they found the same results with the addition of a marked rise in blood pressure. De-Valera and Keller,<sup>20</sup> in England, made a comparable study with about the same results. In an investigation of nonpregnant and pregnant normal women, pre-eclamptics, and patients during the puerperium they found that the most marked response to posterior pituitary extract was obtained in the pre-eclamptic group, and this was followed by the non-pregnant and puerperal group with the least significant reaction obtained in the normal pregnant women who proved to be relatively insensitive to the drug. Our patient received ephedrine sulfate, 50 mg., with novocain when a skin wheal was raised for spinal puncture. This fact is important because of the work reported in 1931 by Melville and Stehle.<sup>21</sup> These investigators found that the vasopressin action of pituitary is enhanced when its use is preceded by adrenaline or ephedrine. The coronary dilating action of ephedrine thus eliminates the constricting action of the pituitrin with a consequent rise rather than a drop in blood pressure. In other words the nature of the blood pressure response to pituitary extract is determined by the extent and nature of the effect on the coronary vessels which, in our case, were dilated by the use of ephedrine and which probably remained so when the peripheral vessels were constricted by the pituitary extract resulting in a rise in pressure. This case presentation is also interesting in a consideration of the theories promulgated by Hofbauer<sup>22</sup> working experimentally with intravenous pituitary extract in dogs. Hofbauer was able to bring about changes which were similar to those found in the eclamptic state. These phenomena were hyperglycemia, increased lactic acid content, lowering of the CO<sub>2</sub> combining power, and an increase in inorganic phosphates. He postulated that in toxemia there was an excess of posterior pituitary substance which by its known pressor and antidiuretic action brought about a state of anoxemia in the tissues due to interference with oxygenation from angiospasm. Working along the same lines Anselmino and Hoffmann<sup>23</sup> reported an increased amount of posterior pituitary extract in the blood of patients with eclampsia. Teel and Reid<sup>24</sup> working at the Boston Lying-in Hospital have, in some cases, shown the presence of an antidiuretic substance in pre-eclamptics and eclamptics. These findings were not consistent in all cases but were found most often in those cases with pronounced edema. Kustner<sup>25</sup> also



that mentioned above, parenteral fluids, blood transfusions, foreign protein, drainage of abscess, etc.; their hospital stay ranged from one to several weeks (Table II).

TABLE II. CASES ADMITTED TO HOSPITAL PRIOR TO TREATMENT IN O.P.D.

|              | OLD SERIES | NEW SERIES | TOTAL |
|--------------|------------|------------|-------|
| No treatment | 42         | 26         | 68    |
| Treatment    | 19         | 18         | 37    |
| Total        | 61         | 44         | 105   |

TABLE III. NUMBER OF COURSES OF VACCINE (SIX INJECTIONS) GIVEN EACH CASE

| COURSES       | OLD SERIES | NEW SERIES | TOTAL |
|---------------|------------|------------|-------|
| Less than one | 8          | 17         | 25    |
| One           | 122        | 177        | 299   |
| Two           | 35         | 28         | 63    |
| Three         | 5          | 5          | 10    |
| Four          | 1          | 1          | 2     |
| Five          | 1          | 0          | 1     |
| Total         | 172        | 228        | 400   |

Table III presents the number of courses of vaccine that were given to the patients. The majority of our cases (81 per cent) required one course of vaccine or less. An attempt was made to analyze those cases requiring more than one course of treatment and to discover a possible reason for extended treatment. An active infection of the cervix was the most outstanding reason. The need for further treatment and the presence of complications such as phlebitis, hemorrhage, pyelitis, abscess, etc., followed in order (Tables IV and V).

TABLE IV. COMPLICATIONS PRESENT WHEN TWO OR MORE SERIES OF VACCINES WERE GIVEN (400 CASES)

| COMPLICATIONS                 | NUMBER | PER CENT |
|-------------------------------|--------|----------|
| Required treatment            | 26     | 6.5      |
| Chronic cervicitis            | 30     | 7.5      |
| Complications, pyelitis, etc. | 7      | 3.5      |
| Hospitalization advised       | 3      |          |
| Irregular treatment           | 2      |          |
| No treatment necessary        | 1      |          |
| Trichomonas vaginalis         | 1      |          |

TABLE V. COMPLICATIONS PRESENT WHEN THREE OR MORE SERIES OF VACCINES WERE GIVEN (400 CASES)

| COMPLICATIONS                 | NUMBER |
|-------------------------------|--------|
| Required treatment            | 2      |
| Chronic cervicitis            | 9      |
| Complications, pyelitis, etc. | 1      |

Table VI presents the number of months of treatment that were given to the patients. The majority of our cases (75.5 per cent) required one month, or less, of treatment. Tables VII and VIII attempt to analyze the reasons that prolonged treatment beyond one month. Again the outstanding reason was the presence of an active chronic cervicitis; slow response to treatment was next.

# THE TREATMENT OF PELVIC INFLAMMATORY DISEASE WITH INTRADERMAL ADMINISTRATION OF BACILLUS COLI VACCINE

## A SUPPLEMENTARY REPORT

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IN THIS paper 228 additional cases of pelvic inflammatory disease of puerperal and venereal etiology are presented. All were treated by intradermal injections of a vaccine of *B. coli* which contained 3 billion organisms per cubic centimeter. Supplementary operative procedures were performed as they were indicated. The new cases were followed for an average of 7.1 months.

Tables I to X present interesting data in regard to this new material and the old series of 172 cases that were reported in this JOURNAL, January, 1941. Specific details of treatment may be found in that article.

This study led to the following conclusions:

1. Intradermal administration of a suitable and potent foreign protein substance, such as our vaccine, was effective treatment. It was more safe and less uncomfortable to the patient.
2. Adequate medical treatment deserved a trial before resorting to radical surgery in every case.
3. Expertness in diagnosis and judgment in treatment improved with experience.

TABLE I. AGE AND COLOR DISTRIBUTION (400 CASES)

|             | WHITE | BLACK | TOTAL |
|-------------|-------|-------|-------|
| 10-15 yr.   | 2     | 0     | 2     |
| 16-20 yr.   | 26    | 52    | 78    |
| 21-25 yr.   | 48    | 90    | 138   |
| 26-30 yr.   | 29    | 44    | 73    |
| 31-35 yr.   | 23    | 24    | 47    |
| 36-40 yr.   | 7     | 12    | 19    |
| 41-45 yr.   | 3     | 5     | 8     |
| 46-50 yr.   | 0     | 2     | 2     |
| Over 50 yr. | 2     | 2     | 4     |
| No record   | 12    | 17    | 29    |
| Total       | 152   | 248   | 400   |

Table I presents the age and color distribution of our patients. All were indigent and were treated at the out-patient department at Receiving Hospital.

Approximately one-fourth of our patients were admitted to the hospital prior to treatment in the dispensary because of their "acute condition." Those designated as having had "no treatment" received bed rest, cold to abdomen, and sedation; they were discharged in a few days. The cases designated as "treatment" received in addition to

Table IX presents the result obtained by the administration of vaccine alone.

Table X presents the 86 patients that were operated upon following the administration of vaccine therapy. Approximately one-half required the removal of cervical infection to effect a cure; 25 per cent required the drainage of an abscess; the remainder were advised to have abdominal section. Seven patients refused abdominal section because of the disappearance of subjective symptoms even though definite masses could be demonstrated. In the entire series of 400 cases, 6 per cent were advised to have abdominal section but only 4.25 per cent were actually operated upon.

I wish to express my deepest appreciation to my confreres in the clinic, Drs. R. Baer, D. M. Davidow, and F. B. Wight, who carried on the work when they took over the service; to Dr. H. Dibble, who, in the early stages of this investigation, kindly allowed me the use of his in-patient service; to Dr. D. M. Morrill, superintendent, who expedited the handling of case histories by supplying special forms; to Irene Weed who kept such excellent records; and last but not least all of those on the resident staff who did much of the actual detail.

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## ESTROGEN-WITHDRAWAL BLEEDING

### A STUDY OF COMPARATIVE ACTIVITY OF VARIOUS ESTROGENS

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THERE are numerous methods of comparing the relative value of the various estrogenic hormone preparations available commercially. Any evaluation of potency which is dependent on subjective response of the patient is, for obvious reasons, open to criticism. It is not within the province of this case report to discuss the relative merits of any of the usual procedures.

One fairly constant method of studying the response of a patient to estrogens is to produce an estrin-withdrawal type of bleeding. It is recognized that if estrogenic hormone be administered to a castrate whose uterus has been preserved, bleeding will follow regularly after cessation of administering the hormone, provided sufficient estrogen has been given. This method eliminates the subjective response entirely.

This report is concerned with the studies of a surgical castrate over a period of nearly four years. Various estrogens have been administered and evaluated entirely on the objective basis of producing estrin-withdrawal bleeding.

Mrs. G. G., white, 34 years of age.

*Past History:* Pregnancy, in 1936, was complicated by exacerbation of rheumatic fever. Normal baby was born May 9, 1936. In 1938, bilateral cystic ovaries were noted. Operation was performed July 23, 1938. Bilateral pseudomucinous cysts were removed. The postoperative course was uneventful. Within two months after operation, flushes were first noted. Subsequently she noted a fairly constant syndrome of head-

TABLE VI. NUMBER OF MONTHS OVER WHICH VACCINE WAS GIVEN

| MONTHS        | "OLD"<br>SERIES | "NEW"<br>SERIES | TOTAL | PER CENT |
|---------------|-----------------|-----------------|-------|----------|
| Less than one | 3               | 6               | 9     | 75.5     |
| One           | 118             | 175             | 293   |          |
| Two           | 27              | 20              | 47    |          |
| Three         | 10              | 10              | 20    |          |
| Four          | 3               | 3               | 6     |          |
| Five          | 2               | 0               | 2     | 24.5     |
| Six           | 3               | 5               | 8     |          |
| Seven         | 3               | 5               | 8     |          |
| Eight         | 0               | 3               | 3     |          |
| Nine          | 1               | 0               | 1     |          |
| Twelve        | 0               | 1               | 1     |          |
| Fifteen       | 1               | 0               | 1     |          |
| Forty-two     | 1               | 0               | 1     |          |
| Total         | 172             | 228             | 400   |          |

TABLE VII. COMPLICATIONS PRESENT WHEN PATIENTS REQUIRED MORE THAN TWO MONTHS OF TREATMENT (400 CASES)

| COMPLICATIONS        | NUMBER |
|----------------------|--------|
| Required treatment   | 11     |
| Chronic cervicitis   | 25     |
| Posterior colpotomy  | 5      |
| Uterine retroversion | 1      |
| Salpingectomy done   | 2      |
| Hemorrhage           | 1      |

TABLE VIII. COMPLICATIONS PRESENT WHEN PATIENTS REQUIRED MORE THAN THREE MONTHS OF TREATMENT (400 CASES)

| COMPLICATIONS       | NUMBER |
|---------------------|--------|
| Required treatment  | 7      |
| Chronic cervicitis  | 15     |
| Posterior colpotomy | 5      |
| Hemorrhage          | 1      |

TABLE IX. RESULT OBTAINED FROM VACCINE ALONE

|            | "OLD"<br>SERIES | "NEW"<br>SERIES | TOTAL | PER CENT |
|------------|-----------------|-----------------|-------|----------|
| Cured      | 133             | 158             | 291   | 72.75    |
| Improved   | 35              | 59              | 94    | 23.50    |
| Unimproved | 4               | 11              | 15    | 3.75     |
| Totals     | 172             | 228             | 400   | 100.00   |

TABLE X. OPERATIVE PROCEDURES IN 400 CASES

|                     | "OLD"<br>SERIES | "NEW"<br>SERIES | TOTAL | PER CENT |
|---------------------|-----------------|-----------------|-------|----------|
| Posterior colpotomy | 12              | 4               | 16    | 4.7      |
| Other abscesses     | 3               | 0               | 3     |          |
| Polyps removed      | 0               | 3               | 3     |          |
| Conization          | 12              | 9               | 21    | 10.0     |
| Cautery             | 12              | 6               | 18    |          |
| Sturmdorf           | 0               | 1               | 1     |          |
| Abdominal sections  |                 |                 |       |          |
| 1. Performed        | 7               | 10              | 17    | 4.25     |
| 2. Refused          | 3               | 4               | 7     | 1.75     |
| Totals              | 49              | 37              | 86    |          |

ache, tightness in the ears, weakness, and flushes. From October, 1938, to April, 1939, the patient received intermittent injections of various commercially available estrogens with varying subjective response. Since April, 1939, treatment consisted of oral administration of estrogens.

Table I reveals the detailed observations of type of medication, dosage, duration of treatment, and response during the past three years.

Above a certain minimum, there does not seem to be such a close relationship in this patient between an increase in amount of medication and the subjective response.

The subjective response to stilbestrol was very unsatisfactory. It has been our general observation that 1 mg. is sufficient to control the average menopausal syndrome. In this patient such was not the case, and when the dose of stilbestrol was raised sufficiently to result in bleeding upon withdrawal, severe nausea resulted.

The response to alpha estradiol was most constant. When the total dosage over a three weeks' period was less than 50.0 mg., the subjective response was uniformly poor, although a scant bloody flow might ensue. With dosage about 50.0 mg. in three weeks, the sense of well-being was best and the flow on withdrawal was best.

Alpha estradiol administered sublingually in solution in propylene glycol seemed to be about three to four times as potent as when taken by mouth in tablet form.

Ethinyl estradiol has proved to be the most active estrogen studied in this series. Using withdrawal bleeding as a criterion of activity, ethinyl estradiol is approximately fifty to seventy-five times as active as alpha estradiol, both administered orally.

The doses which controlled the menopause syndrome best subjectively were those which produce estrin-withdrawal bleeding.

#### CONCLUSIONS

1. Estrogen-withdrawal bleeding may be employed as an index of objective response to estrogen therapy.

2. Using estrogen-withdrawal bleeding as a criterion of activity, stilbestrol, estriol, alpha estradiol tablets, alpha estradiol in solution in propylene glycol and ethinyl estradiol were administered to a patient who had both ovaries removed surgically.

3. Ethinyl estradiol was the most active estrogen used. Alpha estradiol in propylene glycol, sublingual, was the next most active. Alpha estradiol, estriol and stilbestrol were of about equal potency in the dosage administered orally.

4. The best subjective response was obtained with maximum doses of alpha estradiol, and with minimal doses of ethinyl estradiol.

The alpha estradiol and ethinyl estradiol used in this study were supplied by Dr. Max Gilbert of the Schering corporation.

TABLE I

| PREPARATION<br>USED                                    | DAILY<br>DOSE                   | NO. OF<br>DAYS OF<br>TREAT-<br>MENT | TOTAL<br>MG. OF<br>MEDICA-<br>TION | RESULTS  |  |
|--|---------------------------------|-------------------------------------|------------------------------------|--|--|
|  |                                 |                                     |                                    | OBJECTIVE  | SUBJECTIVE                             |
| Stilbestrol (oral)                                     | 1.0 mg.                         | 10 days                             | 10.0 mg.                           | No bleeding  | No improve-<br>ment                    |
| Stilbestrol (oral)                                     | 4.0 mg.                         | 13 days                             | 52.0 mg.                           | Bleeding 5 days<br>after cessation                 | Severe<br>nausea                       |
| Stilbestrol (intra<br>M)                               | 5.0 mg.<br>every other<br>day   | 6 days                              | 15.0 mg.                           | No bleeding  | Nausea                                 |
| Mixed estrogens*<br>(intra M)                          | 10,000 I.U.<br>every 4th<br>day | 10 days                             | 40,000 I.U.                        | No bleeding  | Good                                   |
| Mixed estrogens*<br>(intra M)                          | 15,000 I.U.<br>1 x week         | 48 days                             | 110,000<br>I.U.                    | No bleeding  | Fair                                   |
| Mixed estrogen†<br>(oral)                              | 18,000 I.U.                     | 20 days                             | 360,000<br>I.U.                    | Good flow 7 days<br>after cessation                | Poor                                   |
| Alpha estradiol<br>(oral)                              | 1.5 mg.                         | 20 days                             | 30.0 mg.                           | Cramps. No bleed-<br>ing                           | Good                                   |
| Alpha estradiol<br>(oral)                              | 2.0 mg.                         | 16 days                             | 32.0 mg.                           | Cramps. No bleed-<br>ing                           | Good                                   |
| Alpha estradiol<br>(oral)                              | 3.0 mg.                         | 21 days                             | 63.0 mg.                           | Flowed 6 days<br>after cessation.<br>Flowed 5 days | Excellent                              |
| Alpha estradiol<br>(oral)                              | 3.0 mg.                         | 21 days                             | 63.0 mg.                           | Flowed 5 days<br>after cessation                   | Excellent                              |
| Alpha estradiol<br>(oral)                              | 3.0 mg.                         | 14 days                             | 42.0 mg.                           | Sl. brownish stain<br>5 days after ces-<br>sation  | Good                                   |
| Alpha estradiol<br>(oral)                              | 2.5 mg.                         | 21 days                             | 52.5 mg.                           | Scant flow 6 days<br>after cessation               | Good                                   |
| Alpha estradiol<br>(oral)                              | 2.5 mg.                         | 21 days                             | 52.5 mg.                           | Brownish stain 5<br>days after cessa-<br>tion      | Fair                                   |
| Alpha estradiol<br>(oral)                              | 3.0 mg.                         | 21 days                             | 63.0 mg.                           | Spotty flow 7 days<br>after cessation              | Excellent                              |
| Alpha estradiol<br>(oral)                              | 2.5 mg.                         | 20 days                             | 50.0 mg.                           | Flow 4 days after<br>cessation                     | Good                                   |
| Alpha estradiol<br>(oral)                              | 2.5 mg.                         | 20 days                             | 50.0 mg.                           | Flow 7 days after<br>cessation                     |  |
| Alpha estradiol<br>(oral)                              | 1.5 mg.                         | 20 days                             | 32.5 mg.                           | Brownish stain                                     | Poor                                   |
| Alpha estradiol<br>(oral)                              | 1.5 to 2.0<br>mg.               | 20 days                             | 37.5 mg.                           | No flow  |  |
| Alpha estradiol in<br>propylene glycol<br>(sublingual) | 0.5 mg. (1.0<br>c.c.) plus      | 21 days                             | 12.5 mg.<br>(25 c.c.)              | 3 days after cessa-<br>tion—cramps                 | Not as good<br>as to oral              |
| Ethinyl estradiol<br>(oral)                            | 0.1 mg.                         | 6 days                              | 0.6 mg.                            | No bleeding  | Severe<br>nausea and<br>vomiting       |
| Ethinyl estradiol<br>(oral)                            | 0.05 mg.                        | 21 days                             | 0.85 mg.                           | Good flow 7 days<br>cessation                      | Excellent<br>but<br>bloated;<br>nausea |
| Ethinyl estradiol<br>(oral)                            | 0.05 mg. q<br>other day         | 21 days                             | 0.45 mg.                           | No flow  | Fair                                   |
| Ethinyl estradiol<br>(oral)                            | 0.05 mg.                        | 21 days                             | 0.65 mg.                           | Good flow 6 days<br>after cessation                | Headache<br>Nausea                     |

\*Amniotin, Estrolin.

†Urestrin, Upjohn (estrogenic hormone, oral).



## VARIATIONS IN THE ELECTROENCEPHALOGRAM DURING THE MENSTRUAL CYCLE\*

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WHILE studying the correlation between brain potentials and other variables, such as heart rate, blood pressure, and metabolic rate, Lindsley and Rubenstein<sup>1</sup> found that in four cases the alpha frequency varied greatly during the midmenstrual period. They did not report, however, that there is a relation between brain potentials and the menstrual cycle. The present study was undertaken because such a relation seemed possible. This possibility was strengthened by the observation of Irving, Reid and Gibbs<sup>2</sup> that the electrical activity of the cerebral cortex is slowed during pregnancy.

### MATERIAL AND METHOD

Daily electroencephalograms of 11 healthy young women were obtained during at least one menstrual cycle. The activity of the right frontal, parietal, and occipital areas (indifferent electrodes on the ear) was recorded with a three-channel Grass electroencephalograph. At the same time, the activity of the right occipital area was recorded as a shadowgram on film. A strip of this shadowgram, thirty seconds in duration, was analyzed into a spectrum with the Grass frequency analyzer.<sup>3</sup>

### RESULTS

Day-to-day variations in the electrical activity of the cortex occurred in all cases. Changes were evident in the ink record, but they were most easily demonstrated in the spectra. Therefore, the data presented here are based entirely on successive-day comparisons of spectra. Each column in Figs. 1 and 2 represents a change in frequency from the preceding day. These deviations in frequency were determined as follows: The spectrum for a given day was placed on a transilluminator and the spectrum for the succeeding day laid over it. The attempt was made to obtain a maximal superimposition of the two curves by a displacement on the frequency scale. For example, if it was found after trial that when the curve for the succeeding day was shifted one-half cycle to the fast side, a maximal superimposition of the two curves was obtained, then the change was reported as a deviation of  $\pm 0.5$  cycle per record. In order to reduce the error introduced by subjective factors, spectra were compared by three observers independently without knowledge of

\*This study was aided by grants from the John and Mary R. Markle and the Rockefeller Foundations. Spectrum analysis was carried out with the aid of the Work Projects Administration under Official Project No. 165-2-00-3.



## SUMMARY AND CONCLUSIONS

Successive-day comparisons of the electrical activity of the cortex of 11 healthy young women revealed no simple rigid relation between the electrical activity of the cortex and the menstrual cycle, but in the majority of women this activity becomes slower after the beginning of the menstrual flow, and in some a disturbance in frequency regulation occurs at the midmenstrual period.

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## THE COLOSTRUM TEST FOR PREGNANCY IN A PRENATAL CLINIC

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THE colostrum test has created so much discussion since the original paper by Falls, Frieda, and Cohen in this JOURNAL (41: 431, 1941), that we decided to try it out in the prenatal clinic at the Harlem Hospital in New York City. Because no mention was made of the reactions in the colored as compared with the white race, we felt that this study would bring out interesting results. The only prerequisite was registration in the prenatal clinic.

Although this series was started in July, 1941, we waited until all of the patients could be checked clinically for a definite diagnosis before submitting our results.

Previous to the publication of our paper, Goldman, Kessler and Wilder, at the Newark Beth Israel Hospital, reported a series of cases in the *Journal of the American Medical Association* (119: 130, 1942). They followed the procedure of study of the original authors (Falls, Frieda, and Cohen), while we confined ourselves exclusively to patients attending the prenatal clinic.

We followed the original authors' technique with one exception. To rule out the possibility of a reaction to the merthiolate, we added a solution of merthiolate to both the colostrum and the saline control. We were rewarded for this precaution by having two cases that gave us a definite positive reaction to both the colostrum and the saline control. To eliminate further the possibility of error, all injections were

3. The onset of menstruation was followed by slowing in nine out of 11 cases (all cases except 3 and 4).

4. Shifts in frequency possibly related to ovulation occurred in the mid-menstrual period in eight of 11 cases (Cases 1, 2, 3, 5, 7, 8, 10 and 11). In 7 of the 11 cases, slowing occurred on either the midmenstrual day or the day after the midmenstrual day (Cases 2, 3, 5, 6, 7, 9 and 11).

#### DISCUSSION

These findings do not indicate a simple, rigid relation between the menstrual cycle and the electrical activity of the cortex, but they do indicate that sufficient slowing can occur in association with menstruation to change a normal electroencephalogram to an abnormal one. Differences in frequency of one-half cycle are significant. Such differences have been correlated with differences in behavior (4, 5, 6).

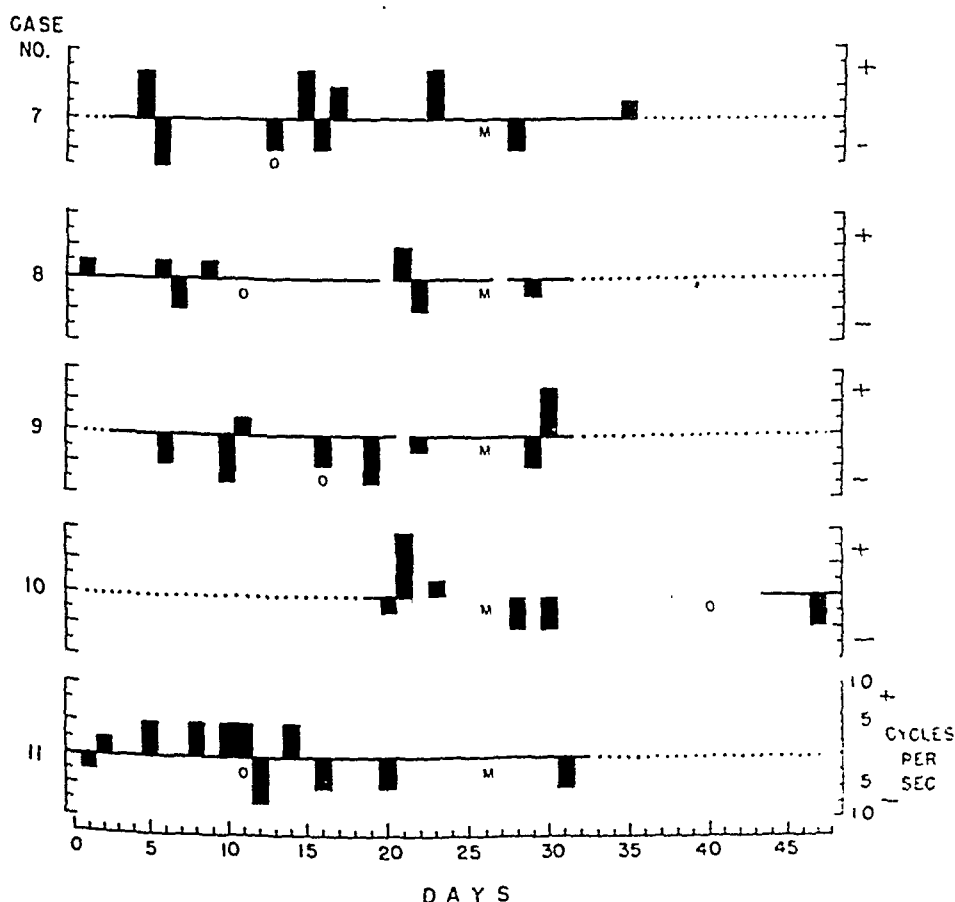


FIG. 2.

In view of these findings it seems reasonable to suppose that the changes in mood and efficiency commonly associated with the menstrual period may be related to modifications of central nervous function, modifications which may also manifest themselves in a change in the electrical activity of the cortex.

Therefore we considered these as negative in our final computations:

|                                     | Total number | 61 |
|-------------------------------------|--------------|----|
| 1. Total number correct diagnoses   |              | 55 |
| 2. Total number incorrect diagnoses |              | 2  |
| 3. Total number not checked         |              | 4  |

Eliminating Group 3, we get 96.5 per cent correct diagnoses and 3.5 per cent incorrect diagnoses.

Adding Group "A" and Group "C" we have the following:

|                                     |     |
|-------------------------------------|-----|
| Total number of negative results    | 190 |
| Total number of correct diagnoses   | 185 |
| Total number of incorrect diagnoses | 5   |

Thus we may conclude that if we get a definitely negative result as in Group "A" or a doubtful reaction as described in Group "C," we have 97.4 per cent correct diagnoses for pregnancy and 2.6 per cent incorrect diagnoses.

In this series there were 197 definitely pregnant women in whom the colostrum gave a correct diagnosis in 94 per cent and an incorrect diagnosis in 6 per cent. There were also 9 nonpregnant women in whom we made a correct diagnosis with colostrum in 44 per cent and a wrong diagnosis in 56 per cent.

Thus we find that in a negative reaction to the colostrum, the test will be correct as a positive diagnosis of pregnancy in 97.4 per cent of the cases. On the other hand, a positive reaction to the colostrum is only 25 per cent reliable in making a diagnosis of nonpregnancy. Whereas pregnant patients will give a correct reaction to the colostrum in 94 per cent of the cases, nonpregnant ones will react correctly in only 44 per cent of the cases. Therefore, we must admit that the test is of definite value when we get a negative reading and of no value where the result is positive.

We had occasion to use the Friedman modification of the Aschheim-Zondek test for a check in 13 cases. Our results are tabulated in Table I.

TABLE I

| COLOSTRUM TEST |          |         |         |          | ASCHHEIM-ZONDEK TEST |         |                                     |
|----------------|----------|---------|---------|----------|----------------------|---------|-------------------------------------|
| NO.            | DATE     | READING | RESULT  | DATE     | READING              | RESULT  | CLINICAL DIAGNOSIS                  |
| 217            | 12/19/41 | Neg.    | Correct | 11/25/41 | Neg.                 | Wrong   | Pregnant 2 months                   |
|                |          |         |         | 12/26/41 | Pos.                 | Correct |                                     |
| 187            | 12/ 4/41 | Pos.    | Correct | 12/ 1/41 | Neg.                 | Correct | Amenorrhea 5 months                 |
| 216            | 12/16/41 | Neg.    | Wrong   | 10/27/41 | Neg.                 | Correct | Amenorrhea 8 months                 |
| 158            | 11/25/41 | Pos.    | Correct | 10/31/41 | Neg.                 | Correct | Sterility 10 years                  |
| 177            | 11/28/41 | Neg.    | Wrong   | 11/28/41 | Neg.                 | Correct | Amenorrhea 9 months                 |
| 183            | 11/28/41 | Neg.    | Correct | 10/29/41 | Pos.                 | Correct | Pregnant 5 months                   |
| 146            | 10/27/41 | Pos.    | Correct | 10/30/41 | Neg.                 | Correct | Amenorrhea 3 months                 |
| 152            | 11/21/41 | Neg.    | Correct | 10/ 4/41 | Pos.                 | Correct | Pregnant 5 months                   |
| 115            | 10/20/41 | Pos.    | Correct | 10/28/41 | Neg.                 | Correct | Amenorrhea 2 months                 |
| 91             | 8/15/41  | Neg.    | Correct | 2/ 6/41  | Pos.                 | Correct | Pregnant                            |
| 102            | 9/ 7/41  | Pos.    | Wrong   | 9/26/41  | Neg.                 | Wrong   | Threatened abortion                 |
| 37             | 7/22/41  | Neg.    | Wrong   | 10/16/41 | Neg.                 | Correct | Amenorrhea. Bilateral salpingectomy |
|                |          |         |         |          |                      |         | Pituitary disease                   |
| 29             | 7/18/41  | Neg.    | Wrong   | 2/15/41  | Pos.                 | Wrong   |                                     |
|                |          |         |         | 5/26/41  | Neg.                 | Correct |                                     |

done by one of us. One-fiftieth of 1 c.c. of a solution of equal parts of human colostrum and saline was injected intradermally in the volar surface of the forearm.

We divided our results into three groups as follows:

Group "A": Patients who gave a definite negative reaction to colostrum.

Group "B": Patients who gave a definite positive reaction to colostrum.

Group "C": Patients with a doubtful reaction.

A reaction was considered negative if there was no areola or a very slight areola and no wheal or a wheal smaller than in the original injection. A reaction was considered positive if there was an areola one inch or larger, a wheal larger than the original injection and pseudopods.

The size of the wheal was not consistent except in the definitely negative reaction group. Some of our positive results not only had a larger wheal than the originally described reaction together with pseudopods and an areola of at least one inch in diameter but also a much larger area of edema underlying and surrounding the entire site of injection.

It is our opinion that the size and intensity of the areola should be the primary determining factor in the reading of the results.

We classified our results under the headings of age, color, gravida, parity, Wassermann reaction, trimester of pregnancy, and any medical or surgical complications. We are wholly in agreement with the original authors in that none of these seems to have any bearing on the result.

#### RESULTS

Group "A".—Those with a definite negative reaction, i.e., pregnant:

|   | Total number | 143 |
|---|--------------|-----|
| 1. Total number correct diagnoses   |              | 130 |
| 2. Total number incorrect diagnoses   |              | 3   |
| 3. Total number of whom we lost track or could not establish a definite diagnosis |              | 10  |

If we eliminate Group 3 in our calculations, we find that we have a correct diagnosis of 97.7 per cent and an incorrect diagnosis of 2.3 per cent in this group.

Group "B".—Those with a definite positive reaction, i.e., nonpregnant:

|                                     | Total number | 16 |
|-------------------------------------|--------------|----|
| 1. Total number correct diagnoses   |              | 4  |
| 2. Total number incorrect diagnoses |              | 12 |

In this group we find 25 per cent correct and 75 per cent incorrect diagnoses.

Group "C".—Those giving a doubtful reaction.

Here the areola was pale, less than one inch in diameter and either did or did not have a suggestion of pseudopods. Due to the great number that gave such a reaction, we felt that charting them merely as doubtful or inconclusive would eliminate a great number of cases from our series.

## UTERINE TONUS DURING LABOR

### TOCOGRAPHIC OBSERVATIONS UPON A PATIENT EXPERIENCING ABRUPTION OF THE PLACENTA

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**R**ECENTLY we registered the uterine contractions of a series of patients at frequent intervals throughout labor with a Lóránd tocograph. One patient experienced an abruption of the placenta. The unusual character of this individual's tracing seemed to warrant its being placed on record.

#### CASE REPORT

Patient A. M., colored, aged 37 years, para xi, received prenatal care from the thirtieth week of gestation onward. Previous to this pregnancy she had experienced a mild hypertension. On her first clinic visit, her blood pressure was 140/96. One week before admission, however, it was only 110/80.

At the fortieth week of pregnancy, she was admitted to the hospital with a history that vaginal bleeding had started forty-five minutes earlier. She had felt no fetal movements following the onset of bleeding. Examination revealed signs of incipient shock; the blood pressure was 90/70; hemoglobin, 72 per cent; and urine showed 3+ albumin. The uterus was tense, and fetal heart sounds were absent. There was a slight trickle of blood coming from the vagina. The cervix was 3 cm. dilated and one-half effaced, and the membranes were intact. No placental tissue could be felt within 3 cm. of the internal os.

The membranes were punctured. Seven and one-half hours after the amniotic fluid was drained away, a stillborn infant, weighing 3,200 Gm., was delivered spontaneously. The placenta and about 1,000 c.c. of clotted blood were expelled immediately. Following this, some slight bleeding continued, and the patient soon went into severe shock. In spite of applying the usual measures, including transfusion, the patient died within one hour of delivery. Post-mortem examination revealed a large flabby uterus with a rupture 3 cm. in length in the right side of the lower uterine segment, and an extensive subserosal suffusion of blood extending along the distribution of the large uterine vessels. There was no bleeding into the abdominal cavity.

The tocographic tracings are reproduced in Fig. 1, where their timing in relation to the labor is noted. Each tracing begins at the left. The tocograph was placed upon the patient at "a" where the graph leaves the base line, and removed at "b". Tracing 1 was of thirty-three minutes' duration. The horizontal line above each graph marks the highest point to which it can rise.

#### COMMENT

We were fortunate, in this case, to secure records of uterine activity which covered practically the entire period from the time that the abrup-

In view of the fact that Cases 217 and 29 gave two contradictory Aschheim-Zondek reports, we eliminated them in our final calculations.

Thus in our small series of 11 cases where a clinical diagnosis could not be made, the colostrum test was correct in 7 (63.6 per cent) and wrong in 4 (36.4 per cent).

The Aschheim-Zondek test was correct in 10 (90.1 per cent) and wrong in 1 (9.9 per cent).

Even in this small series the tremendous advantages of the Aschheim-Zondek test over the colostrum test are very amply illustrated.

#### DISCUSSION

In this series we made readings at fifteen minutes, thirty minutes, and one hour. We found that many reactions were indefinite in the first half hour and then became either definitely positive or negative. We found it therefore more advantageous to take our final reading at the end of one hour.

The technique of the test is simple but from our experience the interpretation is difficult. Falls, Frieda, and Cohen read their results as positive, negative, and doubtful. Goldman, Kessler, and Wilder divided them into one-plus, two-plus, three-plus, and four-plus. They called all reactions above two-plus positive. In this series we listed them as positive if the areola was over one inch in diameter and negative if there was no reaction or a very slight one. We considered the doubtful cases as negative. This may account for the high percentage of correct diagnoses in the group of negative reactions.

Although it is very simple to read a definite negative reaction or a definite positive reaction, so many gave a doubtful reaction (61) that a fair amount of experience is needed to differentiate between a positive and a doubtful reaction. One of the disadvantages of the colostrum test, therefore, is the difficulty of interpreting the final reaction.

It was our purpose in this paper to attack this problem from a clinical point of view and from the point of view of the general practitioner who in the last analysis still diagnoses and treats the vast majority of pregnant women.

#### CONCLUSIONS

1. A negative reaction is 97.4 per cent accurate in diagnosing actual pregnancy.
2. A positive reaction is 75 per cent incorrect in the diagnosis of non-pregnancy.
3. In pregnant women the colostrum test will give a correct (negative) reaction in 94 per cent of the cases.
4. In nonpregnant women the test is 56 per cent wrong.
5. The test lacks the accuracy and reliability of the Aschheim-Zondek test in doubtful cases.
6. It would be misleading to consider a positive reaction as either definite or presumptive evidence of the nonpregnant state.

going on in the uterus than can be gathered from simple physical examination of the abdomen.

*Influence of Draining Away of Amniotic Fluid Upon Uterine Activity.*—The membranes were punctured twenty-seven minutes after Tracing 1, Fig. 1 was begun, and eighteen minutes before Tracing 2 was started. No significant drop in tonus followed this operation. The lowering of tonus observed in Tracing 2 was of only slight and temporary nature; this decrease may have been more apparent than real, since the tocograph was removed from the patient before the membranes were punctured. The membranes have ruptured spontaneously during the taking of tocographic tracings of a number of other patients, and this has had no significant effect upon their graphic records.

*Relation of Type of Activity to the Progress of Labor.*—Although the present patient experienced no significant intermittent contractions while any of the tracings were being made; nevertheless, her cervix effaced and dilated. This experience raises the question as to whether the contractions are necessary for the opening of the cervix. Perhaps, they do not play as important a role in this connection as we have assumed in the past. The question requires further study, but the present observations suggest that the intermittent contractions are not necessary.

# 1,620

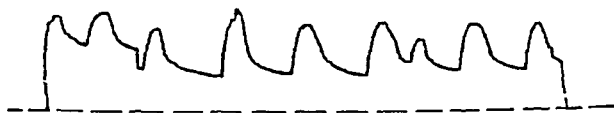


Fig. 2.—Tocographic record of uterine activity of patient who experienced normal labor. Compare with Fig. 1.

*Definition of the Term Tonus.*—Students of uterine motility, unfamiliar with tocographic recording, raise the question as to just what is being measured by the distance of the graph above the base line. Does it represent faulty technique, distention by the uterine contents, or actually the tenseness of the uterus?

What we term tonus does not appear to be due to the tightness of the belt holding the tocograph in position, since the record is not influenced by altering the tightness of the elastic belt. In fact, equally satisfactory measurements are secured if the belt is not employed.

The thickness of the abdominal wall plays little, if any, role in recording tonus. We have secured satisfactory records of tonus from a patient weighing 267 pounds. The magnitude of the uterine contents, likewise, do not appear to influence tonus appreciably. In the case of twin pregnancy, one patient may exhibit high, and another patient experience low tonus. In addition to these findings, variations occur in tonus in the same individual at different times.

The uterus of the present patient was extremely hard at all times and the degree of tonus registered by the tocograph appeared to be in proportion to this characteristic. From these observations, we conclude that the tocograph registers the intrinsic activity of the uterine wall.

tion occurred until delivery took place. The opportunity to secure such a series of tracings was exceptional, since we had on hand a team of nurses trained in tocographic recording, and also since the conditions met with in connection with this accident of labor usually are such that cesarean section is performed.

The points of special interest in this case are four: (1) The type of uterine activity associated with abruption of the placenta. (2) The influence of the draining away of the amniotic fluid upon uterine tonus. (3) The influence of the type of activity upon the progress of labor. (4) What is meant by the term "tonus"?

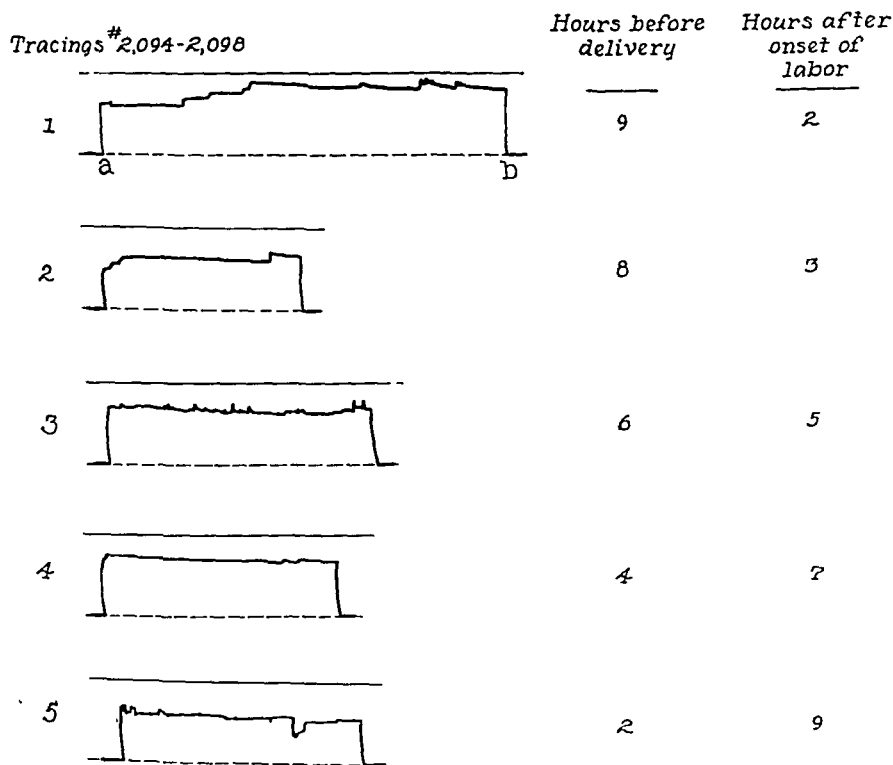


Fig. 1.—Tocographic record of uterine activity of patient suffering from abruption of the placenta. All tracings secured between first signs of abruption and delivery of infant. Tracing begins when tocograph is placed upon patient's abdomen at "a" and ends when it is removed at "b." Note immediate elevation of graph from base line as tocograph is placed in position for recording. This distance is the measure of tonus. Tracing 1 was completed in thirty-three minutes. Note high tonus in all tracings and total absence of intermittent contractions of significant size. Compare tracings of Fig. 1 with Fig. 2. Note lower tonus and the presence of contraction waves in Fig. 2.

*Type of Uterine Activity.*—The chief point of interest in the tocographic tracings of this patient lies in the fact that none of them recorded any evidence of the intermittent contractions which occur so frequently both during late pregnancy and in normal labor. The patient's abdomen was extremely tense at all times before delivery, and this characteristic seems to have been graphically recorded by the tocograph. The type of activity exhibited by the present patient is seen more clearly when compared with a tracing of another patient (Fig. 2) who experienced a normal labor. These findings show how the tocograph may be employed for the purpose of making available a more detailed picture of what is



matic fever, chorea, or pleurisy. She recalled no serious illnesses. Systemic history was essentially negative except as described under present illness.

*Present Illness.*—The patient stated that she “had always had heart trouble” for as long as she could recall. She had shortness of breath on climbing one flight of steps and on walking short distances on level ground. Her finger tips and lips would turn blue after climbing steps. She never had orthopnea or ankle edema. She noticed no increase in the severity of these symptoms with the passing years. She did take physical education in public school, although she experienced shortness of breath after exertion. She had never had any dizzy spells, syncope, or precordial pain.

She was married in April, 1941. Her last menstrual period began May 21, 1941. Previous menses had been normal. She continued to feel well and to do her housework. In July, 1941, she consulted her local doctor. She was told she was pregnant, with estimated date of confinement Feb. 27, 1942. Her heart was not examined at this time, and she was given no special instructions. She pursued her usual activities, and toward the beginning of January, 1942, she began to notice increasing dyspnea on exertion, with an occasional feeling of dizziness. Jan. 11, 1942, she began to notice swelling of her ankles, and also her finger tips and lips turned blue more readily after slight exertion.

*Physical Examination.*—(Jan. 14, 1942.) The patient was a well-developed, well-nourished, 20-year-old, white female. No edema was noted. There was pronounced clubbing of the fingers and suggestive clubbing of the toes. There was moderate to marked cyanosis of the fingers and lips. Respirations were rapid even at rest (26 per minute) with dyspnea on slight exertion. The face was flushed. There was no venous distention. Examination of the head and neck revealed nothing unusual. The patient's chest was well formed and symmetrical. The lungs were normal. Abdominal examination disclosed an intrauterine pregnancy of approximately thirty weeks' duration, with the fetus lying in the vertex position. Fetal heart sounds were heard over the left lower quadrant. The liver and spleen were not palpable.

*Heart:* No unusual precordial pulsations were visible. On percussion the upper left heart border seemed prominent, and the apex of the heart seemed to be displaced somewhat to the left. The right border of the heart could not be percussed beyond the right sternal margin. The point of maximum impulse was in the fifth left intercostal space just outside the mid-clavicular line. There was a coarse systolic thrill and systolic thrust over the third intercostal space next to the sternum, with a visible lift over this area. The heart rhythm was regular, and there were no extra systoles. The heart sounds were forceful and of good quality. At the apex there was heard a loud first sound, followed by a long, high-pitched systolic murmur of moderate intensity. One observer thought there was a slightly blurred accentuated third heart sound early in diastole at the apex. At the base of the heart there was a long, loud, harsh systolic murmur to the left of the sternum in the third intercostal space, rather well localized. The second heart sound over this area was loud, sharp, and ringing. To the right of the sternum over the base of the heart the sounds were not very intense and were essentially similar to those heard to the left of the sternum at this level, except that the second heart sound was not as accentuated. Blood pressure was 132/94. The radial pulses were normal.

## SUMMARY AND CONCLUSIONS

1. The uterine motility of a patient suffering from placental abruption was recorded throughout labor with a Lóránd tocograph.
2. The patient exhibited a persistently high uterine tonus, but at no time any significant intermittent uterine contractions.
3. The following subjects were discussed: (a) The influence of puncturing the membranes upon tonus, (b) the relation of the intermittent contractions to the effacement and dilatation of the cervix, and (c) the definition of the term "tonus."

## PREGNANCY AND LABOR IN A PATIENT WITH CARDIAC ANOMALY, PROBABLE TETRALOGY OF FALLOT

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CONGENITAL heart disease complicating pregnancy is a very uncommon condition. Hamilton and Thomson<sup>1</sup> reported 28 cases of recognized congenital heart disease among 48,190 women delivered at the Boston Lying-in Hospital, an incidence of 1 in 1,721 cases of pregnancy. Mendelson and Pardee<sup>2</sup> listed 20 cases of recognized congenital heart disease in approximately 31,000 obstetric patients at the New York Lying-in Hospital, a frequency of one in about 1,550 obstetric patients.

In the former series there are only 2 cases which fit into the cyanotic group of Maude Abbott; i.e., congenital cardiac defect with cyanosis due to permanent venous-arterial shunt. In the group of patients described by Mendelson and Pardee, there are 8 with pulmonary stenosis, and the authors could find only 25 others reported. In some of these there may have been other associated cardiac defects as well, and in a few instances the existence of the tetralogy of Fallot may be suspected (Case 6 of Mendelson and Pardee;<sup>2</sup> one case [p. 320] of Hamilton and Thomson<sup>1</sup>).

Because of the infrequency of reported cases of congenital cardiac disease complicating pregnancy and because of the paucity of reports of successful childbirth in patients with suspected tetralogy of Fallot, it was considered worth while to describe the following case, in which such a diagnosis was tenable.

### CASE REPORT

V. S. (History No. B-13295), a 20-year-old white female, was first seen in the outpatient department of the Sinai Hospital on Jan. 14, 1942. She was at that time seven and one-half months pregnant and had come to register as an obstetric patient.

*Family History.*—The patient was the sixth of seven children, the others being apparently normal. Her mother died of infection following her last pregnancy. The family history was otherwise essentially negative.

*Past History.*—The patient was born Dec. 15, 1921, following a normal pregnancy. She had had no scarlet fever, pneumonia, diphtheria, rheu-

patient experienced tingling sensations in both hands and fingers after the ether was injected.

*Venous Pressure.*—(Jan. 21, 1942.) 6.75 mm. of water in left arm.

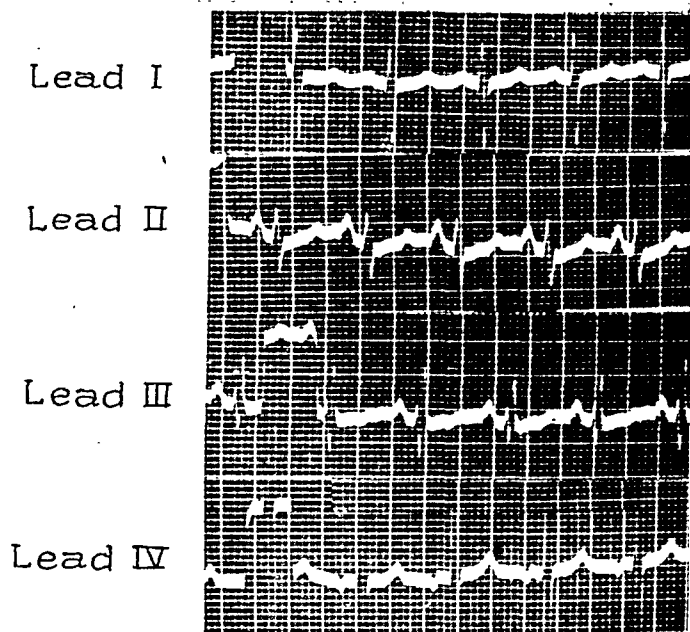


Fig. 2.—Electrocardiogram. Note the right axis deviation and the prominence of the P-waves.

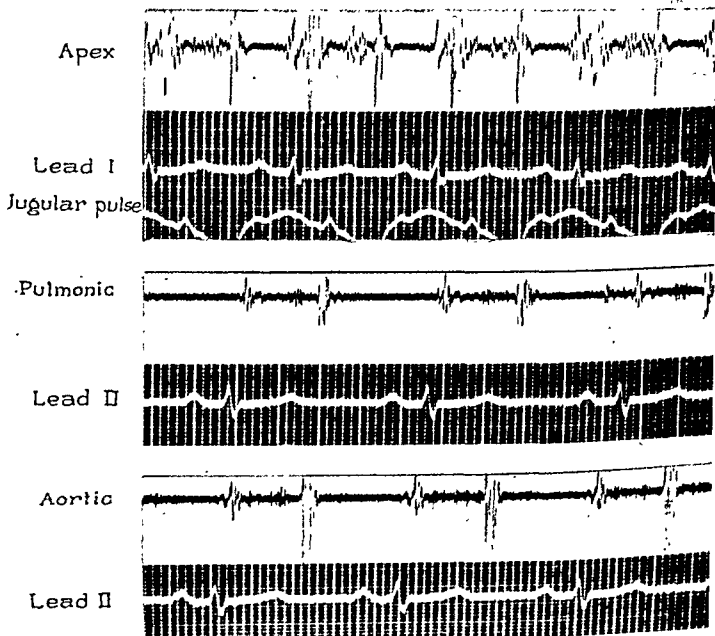


Fig. 3.—Stethogram. *Apex*: Loud auricular sound immediately preceding first heart sound, long systolic murmur, accentuated second heart sound. *Pulmonic*: Long systolic murmur following first heart sound, accentuated second sound. *Aortic*: Similar to pulmonic, but of greater intensity.

*X-ray of Chest.*—(Fig. 1.) The right cardiac border measured 5 cm. and the left 8.6 cm. from the midline. The transverse diameter of the aorta was 4.5 cm. The transverse diameter of the thorax measured 25 cm. There was a fullness of the pulmonary conus, and the heart appeared slightly enlarged. The lung markings were accentuated on both sides with some calcified shadows noted in the hilar regions. (This was a six-foot plate.)

*Fluoroscopic Examination.*—*Posteroanterior view:* The pulmonary conus appeared prominent. The aortic knob seemed normal. There were some small pulsations in the right hilar regions. *Left anterior oblique view:* The right ventricle appeared larger than the left. The aorta seemed normal, and the pulmonary artery could not be visualized. *Right anterior oblique view:* The right ventricle appeared enlarged. The left auricle was normal, and the right auricle was not transected by barium in the esophagus.



Fig. 1.—X-ray of chest. Note the prominence of the pulmonary conus. The heart appears slightly enlarged.

*Electrocardiogram.*—(Fig. 2.) Rate 107 per minute. P-R interval 0.18 seconds. QRS duration normal. Sinus tachycardia. Right axis deviation.  $T_1$ ,  $T_2$  and  $T_4$  upright.  $T_3$  inverted. ST-segments normal. No Q.

*Stethogram.*—(Fig. 3.) *Apex:* There was a loud first heart sound immediately preceded by a loud auricular sound occurring late in ventricular diastole. There was a long systolic murmur of moderate intensity ending in an accentuated second heart sound. There was no definite third heart sound. *Pulmonary area:* The first sound was followed by a long, loud, high-pitched systolic murmur. The second sound was accentuated and high pitched. There were no definite diastolic murmurs. *Aortic area:* The sounds were similar to those over the pulmonary area, but of louder intensity.

*Circulation Time.*—(Jan. 21, 1942.) Arm-to-lung (ether) time was 3.5 seconds. Arm-to-tongue (saccharin) time was 7.0 seconds. The

pregnancy. Thus early examination and diagnosis protect the patient and make possible more complete and better prenatal care.

The pregnant patient with organic heart disease should be examined more frequently than is the nonpregnant patient, for it is known that the burden upon the heart increases as pregnancy advances, reaching a maximum at about the eighth month. In pregnant patients with heart disease, as in similar nonpregnant patients, the indication for digitalis is heart failure. However, it should be noted that increasing dyspnea and tachycardia on exertion and orthopnea may be signs of beginning cardiac insufficiency, and that digitalis may therefore be indicated, especially as the load upon the heart may be expected to increase. If there is any question as to the cardiac condition being the basis for these symptoms, simple methods of determining a prolongation of the circulation and an increase in the venous pressure, more objective evidence of cardiac failure, are easily available. It is not necessary to wait for cyanosis, pulmonary and hepatic congestion and marked peripheral edema to appear before treating the patient for heart failure. Thus, this patient received digitalis not as a routine prophylactic measure, but as a therapeutic procedure.

Bed rest, daily afternoon naps, and restriction of physical activity may be used as prophylactic measures when indicated.

The authors wish to thank Drs. Charles R. Austrian and Helen B. Taussig for their help and suggestions, and Dr. M. W. Aaronson for permission to report this case from the Obstetrical Service.

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## ARTIFICIAL PYREXIA IN FOUR PREGNANT WOMEN

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CUSTOMARY teaching that maternal pyrexia or anoxemia exerts a deleterious effect on the fetus, in utero, has engendered a decided reluctance to induce fever during gestation. By and large sentiment has opposed the practice even when it is otherwise definitely indicated. The results of an inquiry among leaders in the field of physical therapy generally confirmed the truth of this statement although isolated reports of successful treatment of pregnant women were received. In only one instance, abortion, which occurred two weeks after treatment, was reported, but the duration of pregnancy was not stated. Since a dearth of factual information and a considerable controversy exist, a report concerning the results of treatment in four patients should be of value.

In each case, fever was induced by inductothermy with a Burdick fever cabinet. Following a light breakfast, the patient received an

*Laboratory Findings.*—Serologic tests for syphilis were negative. Urinalysis was normal. Blood hemoglobin on Jan. 14, 1942, was 104 per cent of normal.

*Course in Hospital.*—The patient was admitted to the hospital immediately after being examined in the outpatient department. She was put to bed and digitalis was administered. On the day of admission she received 0.6 Gm. of powdered digitalis leaves. At 2:30 A.M. the following morning, January 15, the patient began to have labor pains. She was given a sedative. At 5:30 A.M., after a short labor, she was delivered by low forceps, following a pudendal block and episiotomy, of a live female child in the left occiput anterior position. The child responded immediately. The mother's blood loss was minimal, and repair of the episiotomy was easily accomplished. The child was later found to be entirely normal on physical examination. During the three-hour period of labor and delivery the patient had no unusual tachycardia or dyspnea. Her blood pressure dropped to 124/84 after delivery, and remained within normal limits thereafter. On January 16 the patient was subjected to a Pomeroy sterilization under local anesthesia, and easily withstood this procedure. Digitalization was completed after delivery, and the patient was then maintained on 0.1 Gm. of digitalis leaves per day. She left the hospital on Feb. 7, 1942. Examination six weeks later showed her to be in good general condition, with heart findings essentially unchanged. She was well compensated and was receiving 0.1 Gm. of digitalis leaves daily.

#### DISCUSSION

The clinical diagnosis of tetralogy of Fallot (dextroposition of the aorta, pulmonary stenosis, interventricular septal defect, and right ventricular hypertrophy) is admittedly a difficult one. In the case here described the pulmonary conus is full, rather than absent. The pulmonary stenosis is therefore probably valvular (at the pulmonary orifice) rather than prevalvular (stenosis of the pulmonary conus of the right ventricle). The sensation of tingling in the fingers, following the intravenous injection of the small amount of ether used in determining arm-to-lung circulation time, has been noted in patients with venous-arterial shunts, where some of the ether does not reach the lung; but is shunted to the left heart and reaches the peripheral circulation. Other factors supporting the impression of probable tetralogy of Fallot are the cyanosis and clubbing since birth, the right ventricular enlargement, the right axis deviation of the electrocardiogram, and the rough systolic murmur and coarse thrill at the base of the heart to the left of the sternum.

This case presents several interesting features in the management of obstetric patients with heart disease. The importance of a thorough physical examination of the patient as a routine when she is first seen by the obstetrician should be emphasized. In this case this was not done, and when she was examined at this clinic the patient was found to have organic heart disease and her pregnancy was well advanced, and she presented symptoms of cardiac embarrassment. While the final outcome was not unfavorable, this fortuitous result cannot always be anticipated. If, at the time of examination the patient's cardiac condition is found to be such that pregnancy should be interrupted, this can be accomplished more easily and with less danger to the patient early in

intravenous injection of 800 c.c. of 5 per cent glucose in normal salt solution. Although sedatives were not routinely employed, paraldehyde was administered by mouth if the individual became restless. During the entire stay in the cabinet, oxygen was administered through a nasal catheter. Before return to the ward the intravenous injection of fluid was repeated.

Details of treatment and essential data regarding each patient are included in Table I. It can be seen that the first three patients were treated with considerable caution. Patient 1 (M. K.) was submitted to artificial fever for a total of 22 hours and 30 minutes, with exposure to maximum levels for only 9 hours and 45 minutes. Patient 2 (M. T.) and 3 (B. S.) received artificial fever for totals of  $19\frac{3}{4}$  hours and 10 hours, with exposure to maximum temperatures for  $11\frac{1}{4}$  hours and 6 hours, respectively.

Despite the normal outcome of these three pregnancies and considerable improvement in the basic arthritic condition for which fever was induced, no other patients were treated for two and one-half years. Unquestionably, fear that treatment would inevitably lead to disaster prevented too great enthusiasm. However, the taboparesis of Patient 4 (P. R.) was so far advanced upon admission it was felt nothing could be lost and much might be gained by energetic treatment. Consequently, she received 10 treatments with a total duration of artificial pyrexia of forty-seven hours, and exposure to temperatures above  $104.8^{\circ}$  F. for twenty and one-half hours. Her general condition improved remarkably and the pregnancy was apparently unaffected. Prior to treatment she could not be left unattended, whereas immediately after therapy as well as at her second admission for delivery, her general demeanor was essentially that of a normal woman.

#### DISCUSSION

It has long been recognized that febrile illness, and pneumonia in particular, are prone to produce intrauterine fetal death with subsequent abortion or premature labor. Although the mechanism of the causation of fetal death is unknown, fever and anoxia, among other things, have been indicated. It should be pointed out that febrile illnesses, even those with diurnal swings in the temperature curve, produce a more or less constant fever. This is not the case with artificial pyrexia since the febrile periods are necessarily of short duration. None of the present series of four patients was submitted to artificial fever for more than seven and one-half hours at a single session and in each instance was allowed a minimum recovery period of thirty-six hours before the next treatment.

It is conceivable also that artificial pyrexia may exert a deleterious effect on the embryo or early fetus, without harming one in the second

TABLE I. ARTIFICIAL PYREXIA IN PREGNANCY, TREATMENT DETAILS

| PATIENT             |                 |     |           | TREAT-<br>MENT<br>BEGUN<br>LUNAR<br>MONTH | CONDITION<br>FOR WHICH<br>TREATED | FEVER THERAPY  |  |  |  | LABOR  |  | CHILD                 |                                     |
|---------------------|-----------------|-----|-----------|---|-----------------------------------|--|--|--|--|--|--|-----------------------|-------------------------------------|
| IDENTI-<br>FICATION | HOSPITAL<br>No. | AGE | GRAVIDITY |   |                                   | DATE   | TOTAL<br>DURA-<br>TION*  | DURATION<br>OF<br>MAXIMUM  | MAXIMUM<br>TEMP.   | PULSE  | DATE                                   | LENGTH<br>AND<br>TYPE | WEIGHT<br>(GRAMS)                   |
| No. 1<br>M. K.      | 38-20860        | 20  | i         | 5   | Acute<br>gonorrheal<br>arthritis  | 11/23/37<br>11/27/37<br>12/ 7/37   | 7.15<br>6.45<br>7.30   | 3.00<br>3.30<br>3.15   | 106.8<br>106.4<br>106.8  | 156<br>140<br>157  | 5/26/38<br>15 hr. 30<br>min.<br>Spont. | 3138                  | Female<br>A. and W.<br>at discharge |
| No. 2<br>M. T.      | 39-730          | 23  | i         | 6   | Acute<br>gonorrheal<br>arthritis  | 4/15/39<br>4/18/39<br>4/21/39<br>4/28/39   | 6.00<br>2.45<br>5.15<br>5.45   | 3.00<br>1.25<br>3.45<br>3.30   | 105.0<br>104.9<br>104.6<br>105.5   | 156<br>160<br>162<br>160   | 8/11/39<br>; hr. 50<br>min.<br>Spont.  | 2730                  | Female<br>A. and W.<br>at discharge |
| No. 3<br>B. S.      | 39-14692        | 16  | i         | 9   | Acute<br>gonorrheal<br>arthritis  | 11/11/39<br>11/13/39<br>11/21/39   | 3.30<br>3.45<br>2.45   | 3.45<br>2.00<br>0.15   | 103.6<br>103.5<br>102.0  | 160<br>148<br>136  | 12/20/39<br>73 hr. Low<br>forceps      | 2730                  | Female<br>A. and W.<br>at discharge |
| No. 4<br>P. R.      | 42-360          | 32  | iv        | 7   | Laboparesis                       | 1/22/42<br>1/24/42<br>1/27/42<br>1/30/42<br>2/ 2/42<br>2/ 5/42<br>2/ 7/42<br>2/10/42<br>2/13/42<br>2/16/42 | 3.45<br>3.45<br>4.15<br>4.15<br>5.30<br>4.45<br>4.15<br>4.45<br>6.00<br>5.45 | 2.00<br>2.00<br>2.15<br>2.00<br>2.15<br>2.00<br>1.15<br>2.00<br>2.30<br>2.15 | 104.8<br>105.6<br>104.8<br>104.8<br>105.6<br>105.8<br>105.4<br>105.4<br>105.4<br>105.2 | 144<br>154<br>152<br>148<br>142<br>152<br>144<br>140<br>144<br>152 | 4/18/42<br>; hr. 6<br>min.<br>Spont.   | 3765                  | Male<br>A. and W.<br>at discharge   |

\*Hours and minutes.



to 101°, and pulse around 100. There was a small amount of purulent drainage along the line of sutures in the uterus but the incision healed well.

On March 1 papules about 1 cm. in diameter appeared on the extensor surfaces of the extremities, and the conjunctiva was injected. Sulfathiazole was discontinued and the rash disappeared. The temperature returned to normal in twenty-four hours and remained normal.

On March 17, twenty-six days after the first operation, under general anesthesia, the attachment of the uterus to the abdominal wall was separated and the old incision opened for a distance about two inches above the uterus. The fat in this area was dark in color and showed evidence of old infection. The uterus was dropped back into the abdominal cavity and the abdomen closed, with a drain in the abdominal wall in the area of the old infection. Sulfathiazole was started again. Temperature rose to 101° the following day and 103° on the third day. Skin lesions reappeared at the same site as before so sulfathiazole was discontinued. The temperature immediately fell to normal and remained there throughout her stay in the hospital. Apparently she was very sensitive to sulfathiazole and this caused the rise in temperature.

The wound broke down for a distance of about two inches, corresponding to the area that was above the uterus. The fascia healed well. Since she had one and one-half to two inches of fat in the abdominal wall, it took it some time to granulate and the remainder of her stay in the hospital was necessary because of this. She was discharged April 25, sixty-five days after admission and thirty-nine days after the second operation.

#### COMMENT

This operation should be reserved for those cases of frank infection where the patient is a poor risk for section or where the patient is in her early reproductive life and very anxious to have a child. Since the introduction of the sulfa drugs, it should be considerably safer than formerly. Wound infection is the most frequent complication, and, as illustrated in this case, prolongs the hospital stay.

200 WEST SECOND STREET

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#### ALLERGIC SHOCK CAUSED BY SYNAPOIDIN\*

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**S**YNAPOIDIN is a combination of gonadotropin from human pregnancy urine and extract of anterior pituitary. It is biologically standardized by the method outlined by Mazer and Ravetz<sup>1</sup> in their preliminary report. Emphatic warning is given on the package that this medicament must be used with caution and under close medical observation, since it may cause severe reactions in the form of "enlargement of the ovaries, lower abdominal pain, and tenderness." No mention is made of its possible allergenic quality and examination of the available literature shows no report of shock from its use. Since, according to current medical opinion, the preparation is effective in the treatment of amenorrhea and of dysfunctional uterine bleeding, and its use is be-

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\*A product of Parke, Davis & Company.

or third trimester. Since none of our patients received treatment prior to the fifth lunar month, comment on this point is not justified.

Therapeutic results, even as consistent as these, do not warrant sweeping claims or deductions. On the other hand, it cannot fail to be of general interest that four women in the second and third trimesters of pregnancy were treated by the artificial induction of fever without observable damage to the fetus, in its subsequent intrauterine or early postnatal existence.

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## PORTES CESAREAN SECTION

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**B**ECAUSE of the few instances reported of this operation we add this case to the literature on the subject.

This 21-year-old white woman was admitted to the hospital Feb. 19, 1942, in her second pregnancy and about three weeks from term. Her first pregnancy had terminated spontaneously at seven months and the baby had died shortly after birth.

When first seen her temperature was 100.2° F. and pulse 140. Blood pressure 140/90. She was rather obese. Urine showed a trace of albumin and a few bacteria. The membranes had ruptured thirty-six hours previously and she had been in fairly good labor since. The fetus was lying transversely with the head on the right and the buttocks on the left. The left arm protruded from the vagina almost to the shoulder and was macerated. Her home physician had made unsuccessful attempts to deliver her.

An examination showed the cervix fully dilated and the left shoulder impacted in the pelvis. The uterus was contracted so tightly about the fetus it was impossible to deliver her through the vagina. The fetal heart could not be heard and she stated that she had not felt the baby move since the previous day.

Since the patient was a young woman with no children, was definitely infected, and was in poor condition for a Porro section, we decided to do a Portes operation.

Under general anesthesia the abdomen was opened and the uterus delivered. As the uterus was very wide in the lower part due to the transverse presentation there was nothing to be gained by suturing the peritoneum before the uterus was opened. Tapes were placed around the uterus, and it was opened in the midline. A stillborn fetus was removed and the placenta extracted. The uterus was closed with three layers of continuous sutures. The abdomen was then closed in layers around the uterus.

Wet packs were kept on the uterus and sulfathiazole was started by mouth. There was some abdominal distention during the first twenty-four hours but none thereafter. Temperature was 103.6° F. the following day and pulse still around 140. Temperature thereafter was 100°

no reaction, or a slight and transient irritative response; or, in certain women, a brief blanching of the skin at the site of injection. Evidently no significant quantity of histamine is present in synapoidin. Passive transfer to recipients who showed no reaction to direct testing resulted in immediate and typical positive skin tests in the injected sites, at intervals of from one to five days after receiving the donor's serum.

#### COMMENT

Certain features of this case are of interest, not only to the clinician who may employ synapoidin in treatment, but to students of endocrinology and of allergic disease. This patient became hypersensitive to synapoidin after a therapeutic exposure lasting only seventeen days. Ten days intervened between the third uneventful injection and the fourth, which produced shock. Clinical and dermal sensitivity must have appeared at some time during that ten-day period, in which also the catamenia took place. And this sensitivity was specific to some constituent of the gonadotropic preparation; ample proof of such specificity has been offered. The active constituents are chorionic gonadotropin and pituitary extract, synergistically combined. These are similar to or identical with the secretions of the patient's own endocrine glands. Further, one or both of these hormones must have been relatively deficient, because the synapoidin corrected her dysfunctional bleeding.

Specific sensitivity does not develop overnight in human beings. Repeated adequate exposure is required. Is it possible that this allergic individual had built up a defense against her own hormones, causing their deficiency, and that the three intramuscular doses exhausted her antibodies?

From the clinical angle the matter is less complex. About 10 per cent of American women are actually or potentially allergic. Of these, a certain number will present indications for synapoidin therapy, and undoubtedly some of them will get it. Therefore, it is suggested that caution be exercised in administering this potent biologic preparation to women who have a personal or family history of allergic disease; that the dosage be kept low; and that the diluted material, say 0.02 c.c. of a 1:5 dilution, be used as an intradermal test when, because of the catamenia or for any other reason, a week or more has passed since the preceding dose.

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1105 PROFESSIONAL BUILDING

coming more general, the publication of this report is thought to be desirable.

CASE 1.—A white woman, married, nullipara, aged 40, has for years been subject to perennial allergic rhinitis with seasonal (but not premenstrual) exacerbations. She is not sensitive, either clinically or by skin test, to meat proteins or animal emanations. Her inhalant symptoms are readily controlled by appropriate intradermal therapy with extracts of mold spores and local pollens. On the occasion of one such treatment she remarked that she wished there were "some sort of shot" that would as easily relieve her of another annoyance. Inquiry elicited the following history:

Her menses, which previously had been fairly normal, had in her thirty-first year become excessive, with interval bleeding so severe that anemia developed. Antuitrin-S was used with no result; pituitrin increased both the cramps and the metrorrhagia; theelin had a similar effect. Finally, one application of radium was used. After this, her dysfunctional bleeding ceased, her general health improved, and the menses were normal for several years. When she was 38, the menorrhagia and metrorrhagia recurred briefly, subsiding without treatment; the present recurrence, with almost continuous bleeding, seemed to be growing worse. She had no symptoms of the climacteric.

Synapoidin, 1 c.c. (15 units), was administered intramuscularly on April 25, 28, and May 2, 1942. There was no constitutional reaction. Metrorrhagia decreased after the first dose and ceased after the second. Menstruation, normal in other respects, appeared six days early. It was considered advisable to repeat the course. The patient reported on May 12, received 1 c.c. of synapoidin intramuscularly, and left the office. Our invariable technique of retraction on the plunger, initially and at intervals during the slow injection, was followed. No blood appeared in the syringe, and to the extent that this technique is reliable it is certain that the needle point was not in a vein.

About eighteen minutes later the patient returned, said that she was feeling rather odd, and collapsed. The diagnosis was obvious. A scarlatiniform discoloration was present on her chin and cheeks, dyspnea was marked, and she was in great distress. In spite of an immediate injection of adrenalin, promptly repeated, her anaphylaxis progressed rapidly. The scarlatiniform discoloration spread quickly to the trunk and arms; massive urticaria appeared about the eyes; the extremities quickly became swollen. Waves of nausea were followed by intense abdominal pain, only partially relieved by morphine and atropine. Presently the punctate erythema was replaced by blotches of urticaria, which faded and reappeared as the continuing adrenalin dosage prevailed or failed of control. No rigors had occurred, but later there was profuse sweating. The oral temperature, observed then for the first time, was 100° F.

The patient was kept under observation for six hours, her symptoms gradually subsiding. Nausea, abdominal discomfort, and occasional episodes of urticaria persisted until the following morning.

Four days later she was tested intradermally with a 1:5 dilution of synapoidin. A strongly positive atopic reaction, with typical wheal, flare, and intense itching, appeared in five minutes and persisted for several hours. This same dilution of synapoidin was then used as an intradermal test on a considerable number of children and adults of both sexes. Nearly all of them were known to be allergic. It produced

right side of the vagina. The skin and mucous membrane covering the tumor were purplish red in color, very tense and very painful on palpation.

Under cyclopropane anesthesia, an incision was made over the mass and a large amount of a grayish semisolid gelatinous material was removed. No abscess cavity was seen, nor was there any fluid present. The entire cavity was carefully examined and thoroughly evacuated.

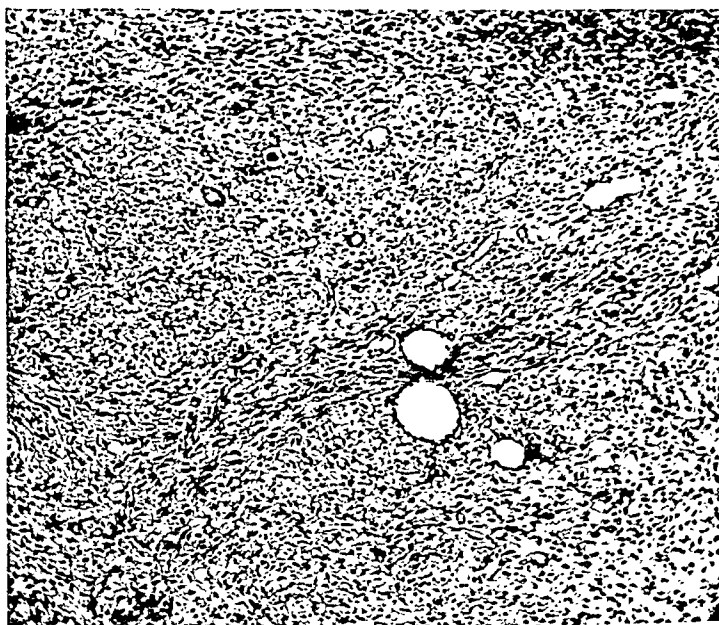


Fig. 1.—No. 18178. Homogeneous, loosely texture connective tissue containing a number of lymphatic vessels and some small blood vessels. Diagnosis: Fibroma.

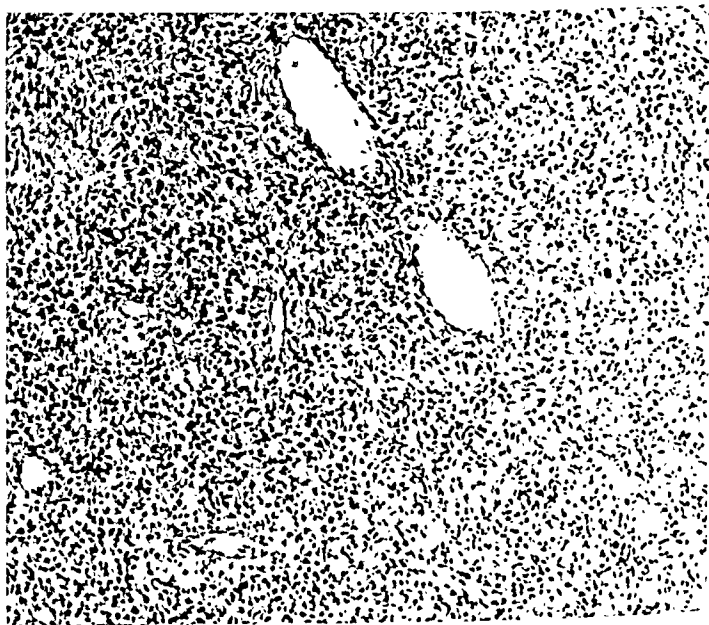


Fig. 2.—No. 21886. Very cellular spindle cell tumor with some areas of myxomatous-like structure and slight tendency to hyperchromatism. Diagnosis: Myxosarcoma.

## A RARE CONNECTIVE TISSUE TUMOR (MYXOSARCOMA) IN THE AREA OF THE BARTHOLIN GLAND

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CONNECTIVE tissue tumors in the area of the vulvovaginal gland are rare and may originate either from vulvar elements or from the terminations of the round ligament. Only two cases of sarcoma of the vulvovaginal (Bartholin) gland have been reported in the literature.<sup>1, 2</sup> Because of the rarity, we wish to report the following case:

Mrs. G. W. (Hospital No. 110,616), aged 44 years, was admitted to the Bronx Hospital service of Dr. Smiley, on April 30, 1940. Aside from a slight thyroid disturbance some seven years earlier which had responded to medical treatment, her past history was essentially negative. She was a gravida iv, para ii, having had one spontaneous miscarriage, one induced abortion, and two normal spontaneous deliveries. Her menstrual history was fairly normal, beginning at the age of 12, with a twenty-seven- to twenty-eight-day cycle, and a flow lasting about five days. Her last regular period was on April 14, 1940, about two weeks before admission to the hospital.

With the ending of this period she began to complain of a burning sensation in the region of the right labia minora, followed soon thereafter by her noticing the presence of a mass. Within the next ten days this mass progressively increased in size. There was no pain.

Physical examination was relatively negative, except for the presence of the tumor situated in the right labium, about the size of a hen's egg, and extending into the right vaginal wall. It felt to be semisolid in character, quite tense but not fluctuant.

Under general anesthesia, the entire mass was easily enucleated on May 1, 1940. She was discharged on May 7, 1940, after an uneventful recovery.

Examination of the specimen (Path. No. 18178) showed a 4 cm. round, pinkish white, well-encapsulated soft mass of tissue which, on section, was soft, yellowish white and homogeneous. Microscopic sections revealed a rather homogeneous, loosely textured connective tissue, containing a number of lymphatic vessels and some small blood vessels. A few mucous glands were present. Diagnosis: Fibroma (Fig. 1).

She was readmitted to the hospital on Dec. 22, 1941 (Hospital No. 129097), with the following history: For the past three weeks there had been considerable pain at the site of the previous operation, for which local applications had been applied with no relief. Several attempts had been made to dilate the duct of Bartholin's gland, without success. Soon thereafter, a small mass appeared which had increased rapidly in size.

Examination at this time revealed the presence of a large, firm non-fluctuant tumor mass, about the size of an orange, which extended upward and bulged into the vagina, occupying more than one-half of the

# ANTE-PARTUM RUPTURE OF THE UMBILICAL VEIN

## REPORT OF ONE CASE

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**I**NTRAUTERINE intra-partum rupture of the umbilical cord has been reported by Bloxsome,<sup>1</sup> Vermelin,<sup>2</sup> Zocchi,<sup>3</sup> Siddall,<sup>4</sup> and Sackett.<sup>5</sup> Complete rupture of the umbilical cord during labor is of more frequent occurrence than is partial rupture which may involve the vein and one or both arteries and result in hematoma formation.

Intrauterine ante-partum rupture of the umbilical vein producing a hematoma of the cord with resulting fetal death has not been reported. This case is presented in illustration of this condition.

The patient was a 25-year-old primigravida. The entire prenatal course was uneventful, and the blood pressure and weight gain were within normal limits.

Two weeks before the estimated date of confinement abdominal and rectal examinations were made. The uterus was enlarged to the size of a term pregnancy, the lie longitudinal, and the presentation cephalic. The fetal heart tones were heard in the lower left abdominal quadrant at the rate of 130 per minute. Three days later the patient reported the absence of fetal motion. Examination at this time showed the lie and presentation to be the same as on the previous examination. The cervix was partially effaced, 2 cm. dilated, and the presenting part was at the level of the ischial spines. Fetal heart tones were not heard and fetal motion was absent.

Labor began spontaneously the following day and the patient entered the hospital. Labor was conducted under sodium amytal and scopolamine analgesia.

Delivery of a stillborn male child was accomplished by prophylactic forceps extraction preceded by a right mediolateral episiotomy under nitrous-oxide-ether anesthesia.

The duration of labor was twelve hours and thirty-five minutes. The first stage was eleven hours, the second stage one hour and 20 minutes, and the third stage fifteen minutes.

At delivery it was noticed that the umbilical cord for a distance of about five inches from the umbilicus was greatly swollen and discolored. The entire cord measured 55 cm. in length, and the placental insertion was central. The stillborn baby, with the exception of slight maceration, appeared normal in form. The cord and placenta were sent to the laboratory for examination with permission for an autopsy upon the baby.

*Laboratory Report.*—The body was that of a well developed male measuring 52 cm. in length. There was some post-mortem liquefaction and degeneration. The placenta and umbilical cord represented the chief pathology. The placenta measured 14 by 13 by 3 cm., and the maternal surface showed the cotyledons to be intact and upon cut sec-

Interrupted chromic catgut sutures were used, to close the entire cavity, and the patient was returned to bed in good condition.

The specimen submitted for pathologic examination (Path. No. 21886) consisted of several irregular portions of grayish yellow gelatinous material. Microscopic sections revealed a very cellular spindle cell tumor with some areas of distinct myxomatous-like structure. There was a slight tendency toward hyperchromatism. *Diagnosis:* Myxosarcoma (Fig. 2).

*Follow-up:* Several courses of deep x-ray therapy were given over the operative site. In February, 1942, she began to complain of back-ache, radiating to the right side. A complete x-ray study was made of her lungs, as well as of the skeletal structures, all of which were negative. She was last seen in April, 1942, at which time there were no complaints. The operative site was free from any pathology.

#### DISCUSSION

The Bartholin gland is surrounded by the perineal fascia and by a coat of striated musculature of which some fasciculi penetrate into the interior of the gland and are located in the connective tissue septa between the lobes of the gland, together with smooth muscle and elastic fibers. Although a genetic relationship between the tumor and the connective tissue which participates in the structure of the gland could not be proved histologically, we feel justified to assume this possibility on the basis of the localization of the tumor and in the absence of proof to the contrary. Clinically, the gradually growing tumor furnished the typical picture of a retention cyst of the gland of Bartholin.

We are indebted to Dr. Joseph Felsen, Director of Laboratories and Medical Research, for the photomicrographs.

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900 GRAND CONCOURSE  
1840 GRAND CONCOURSE



# Department of Practical Problems in Obstetrics and Gynecology

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CONDUCTED BY WILLIAM J. DIECKMANN, M.D.

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## TREATMENT OF HEART DISEASE IN PREGNANCY

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**H**EART disease is one of the most serious complications of pregnancy and responsible for about 10 per cent of all maternal deaths. This, if anything, is a conservative estimate, as indicated by most of the statistics from the maternity hospitals in this country. In our obstetric service, organic heart disease accounts for over 10 per cent of the total maternal mortality.

This paper is based on a study of 676 patients with organic heart disease admitted to the Lying-in Hospital (Woman's Clinic of The New York Hospital) during the period Sept. 1, 1932, to Dec. 31, 1940, although in certain of the data, the statistics for 1941 are included. During the period ending last December, we had 7 maternal deaths from cardiac disease in 34,353 consecutive pregnancies, giving a death rate of 10.3 per 1,000 pregnancies, or a rate five times greater than that for the clinic (1.98 per 1,000).

The incidence of organic heart disease in our obstetric patients was 2.78 per cent during the eight years ending 1940; 676 cardiac patients in 24,289 deliveries.

In the study and management of these patients we have employed the functional classification of the New York Heart Association, which may be described briefly as follows:

- Class I. No limitation of physical activity.
- Class II. Slight limitation of activity.
- Class III. Marked limitation of activity.
- Class IV. Complete limitation of physical activity (bed rest).

Undue fatigue, palpitation, dyspnea and anginal pain are the symptoms of cardiac involvement should the patient exceed the limitation of activity described for each group in this classification. In order to

tion grossly normal. The fetal surface of the placenta was also normal, with the cord taking an approximately central origin. At the fetal end of the cord and continuous with the umbilicus was a large aneurysmal-like thickening and widening of the cord extending over an area measuring 14 cm. in length. In this dilated portion the cord measured  $2\frac{1}{2}$  cm. in one diameter and  $1\frac{1}{2}$  cm. in the other. It was darkly discolored and apparently hemorrhagic in character. Upon cut section the two arteries were found to be of normal size and the walls of the usual thickness. These arteries showed no pathologic changes. About the arteries and completely infiltrating and replacing the myxomatous substance of the cord was an extensive hemorrhage which was dark in color and firm and friable in consistency. The region of the umbilical vein was completely destroyed and replaced by a cavernous type of hemorrhagic sinus which represented a complete rupture of the umbilical vein. Beyond this and toward the placenta, the umbilical vein and arteries were markedly engorged and somewhat dilated. The peritoneal surface of the umbilicus showed no pathological changes. The continuation of the umbilical structures into the urachus and the continuation of the umbilical vessels to the liver showed no anatomic changes and no pathologic conditions.

*Diagnosis.*—(1) Intrauterine rupture of the umbilical vein just proximal to the umbilicus. (2) Massive hematoma of the umbilical vein. (3) Post-mortem liquefaction and degeneration of an otherwise normal fetus. (4) Apparent death in utero.

#### COMMENT

The suggested causes of rupture of the umbilical cord or its component parts are varied. A short cord and syphilis are mentioned most frequently but the accidents reported in which these causes were present occurred during labor. Anomalies of the cord vessels have been suggested as predisposing factors, especially weakness of the vessel walls which rupture especially when the blood is squeezed out of the placenta during a labor contraction.<sup>6</sup> None of the mentioned causes were a factor in this case.

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ever, marked exceptions, where, for example, rheumatic activity exists. In such an instance the grouping may be Class IE.

TABLE III. DISTRIBUTION OF PATIENTS WITH HEART DISEASE ACCORDING TO THE FUNCTIONAL CLASSIFICATION OF THE NEW YORK HEART ASSOCIATION

|           | PATIENTS | PER CENT |
|-----------|----------|----------|
| Class I   | 300      | 44.3     |
| Class II  | 297      | 43.9     |
| Class III | 60       | 8.9      |
| Class IV  | 19       | 2.8      |
| Total     | 676      | 99.9     |

Most of our patients, 88 per cent, were placed in Class I and Class II, as indicated in Table III. These constitute the milder cases of heart disease and ordinarily are not accompanied by a greatly increased maternal mortality. It is the patients in Classes III and IV that cause the greatest concern, not only from the standpoint of mortality, but also with regard to the advisability of continuation of the pregnancy and the method of delivery. It must be pointed out, however, that a patient in Class II, and even one in Class I, may become a serious problem as gestation proceeds, or during and following labor.

From this emphasis placed upon the functional interpretation of heart disease, it must not be concluded that we neglect diagnosis and evaluation of the cardiac lesions. On the contrary, at the first examination of a suspected cardiac patient, a competent cardiologist checks the findings as they relate to the heart. In order to obtain a correct diagnosis as early as possible during gestation and to provide adequate medical prenatal care, we conduct a special cardiac clinic, weekly, under the joint supervision of internists and obstetricians.

Mitral stenosis, either alone or with insufficiency, is usually the most frequent lesion. Rheumatic heart disease accounts for almost 95 per cent of our cardiac patients, while congenital heart disease constitutes about 2 per cent of all organic heart disease. Uncomplicated aortic regurgitation is seen in approximately 3 per cent of the cardiac patients.

The group of women with congenital heart disease complicating pregnancy is relatively small, due no doubt to the fact that the majority of patients with serious congenital cardiac lesions die before the age of puberty. The physician is sometimes consulted regarding the advisability of marriage and pregnancy in patients with congenital heart disease. There can be no doubt that an intelligent answer to this question rests upon a careful evaluation, involving cardiac functional capacity determination, measurement of the size of the heart, consideration of the specific cardiac lesion and estimation of the degree of cyanosis and polycythemia. Mendelson and Pardee conclude that cyanosis *per se* is not a contraindication to pregnancy. In coarctation of the aorta they advise contraception because of definite and increased risk associated

TABLE I. CAUSES OF MATERNAL MORTALITY FOR THE PERIOD SEPT. 1, 1932, TO DEC. 31, 1941

67 Cases in 34,353 Consecutive Pregnancies  
Pavilion, Private, and Outdoor Services

|   | NUMBER OF<br>CASES | PERCENTAGE                 |
|---|--------------------|----------------------------|
| Infection (ante-partum, post-partum, postabortal) | 13                 | 19.4                       |
| Pulmonary complications                           | 10                 | 14.8                       |
| Post-partum hemorrhage                            | 9                  | 13.4                       |
| <i>Cardiac disease</i>                            | 7                  | 10.4                       |
| Pneumonia   | 6                  | 8.9                        |
| Toxemia of pregnancy                              | 4                  | 6.0                        |
| Premature separation of placenta                  | 3                  | 4.5                        |
| Cerebrovascular accident                          | 3                  | 4.5                        |
| Pyelonephritis                                    | 2                  | 3.0                        |
| Circulatory collapse                              | 2                  | 3.0                        |
| Postoperative hemorrhage                          | 1                  | 1.5                        |
| Tuberculosis, miliary                             | 1                  | 1.5                        |
| Placenta previa, ante-partum                      | 1                  | 1.5                        |
| Chorionepithelioma                                | 1                  | 1.5                        |
| Blood dyscrasia, erythroblastic-splénomegaly      | 1                  | 1.5                        |
| Psychosis, reactive panic (suicide)               | 1                  | 1.5                        |
| Peritonitis, after appendicitis                   | 1                  | 1.5                        |
| Not determined, insufficient data                 | 1                  | 1.5                        |
| Total   | 67                 | 99.9                       |
| Total maternal mortality rate                     |                    | 1.98 per 1,000 pregnancies |

TABLE II. INCIDENCE OF HEART DISEASE IN PREGNANCY SEPT. 1, 1932, TO DEC. 31, 1940

|  |                      |
|--|----------------------|
| Total pregnancies, including abortions | 24,289               |
| Patients with classified heart disease | 676 or 2.78 per cent |

determine the amount of physical activity which should be permitted in each case, we have utilized, during the past two years, the following "therapeutic classification," in association with the functioning groupings of the New York Heart Association:

- Class A: Patients with cardiac disease whose physical activity need not be restricted.
- Class B: Patients with cardiac disease whose ordinary physical activity need not be restricted, but who should be advised against unusually severe or competitive efforts.
- Class C: Patients with cardiac disease whose ordinary physical activity should be moderately restricted, and whose more strenuous habitual efforts should be discontinued.
- Class D: Patients with cardiac disease whose ordinary physical activity should be markedly restricted.
- Class E: Patients with cardiac disease who should be at complete rest, confined to bed or chair.

In general, the therapeutic classification follows closely the functional grading of the cardiac capacity, so that the patient in Class I would be given an "A" or "B," in other words. Class IA or IB. There are, how-

Carr and Hamilton report that the incidence of cardiac failure increases steadily from the third to the ninth lunar month of gestation, decreasing during the last month. In our cases, on the other hand, there does not seem to be any particular month of pregnancy when failure is most likely to appear. Congestive heart failure, as stated above, developed in each of the last eight months of pregnancy. Jensen, in a review of a large series of cases, likewise comes to the conclusion that there is no special period of pregnancy when decompensation is most likely to develop.

#### MANAGEMENT OF CARDIAC PATIENTS

As stated above, all cardiac patients are closely observed during the ante-partum period, in a special cardiac clinic. Every obstetric patient having a history of rheumatic fever, chorea, or previous heart disease is referred to this clinic for evaluation even though she may have no symptoms or signs at the moment. Patients with cardiac murmurs, dyspnea, unexplained ankle edema, or tachycardia are referred to this clinic. Each patient is carefully evaluated, laboratory tests, including determination of the vital capacity, electrocardiograms, and roentgenograms at a distance of 7 feet, being performed as indicated. The hemoglobin and cell volume are determined routinely, and the pulse and respiratory rate recorded.

Activity is restricted as indicated. This is especially necessary in the last trimester, although it may be indicated throughout pregnancy. At times, social service assistance with a housekeeper is employed. At times, especially since many of our patients lived on the top floor of apartment buildings (without elevators), it became necessary to urge moving to a ground floor apartment.

Patients seen in the first trimester of pregnancy with serious heart lesions are immediately admitted to the hospital for consideration of interruption of the pregnancy. Upper respiratory infections are regarded ominously, and the patient is frequently admitted for this indication, since experience teaches that this complication may precipitate a break in compensation. As term is approached, certain patients are admitted for rest and evaluation before delivery. This is especially valuable with regard to the mode of delivery.

Digitalis is not employed routinely. It is given on indication. Digitalization is accomplished usually in twenty-four hours. Ordinarily, this drug is given when required, and is not employed prophylactically. Pulse and respirations are charted during labor, and are of particular prognostic significance during the first stage of labor, as will be shown later.

Delivery was effected with the use of basal analgesia and local infiltration in a large number of patients having either spontaneous or operative delivery. This technique is a modification of that used by Urnes and Timmerman and has been described by me, as well as by my associates, Griffin and Benson. Local infiltration anesthesia is also frequently used

with pregnancy in this condition. Should the patient be pregnant, therapeutic abortion is indicated unless the pregnancy is too far advanced, in which event cesarean section and tubal sterilization should be considered.

As rheumatic heart disease accounts for over 90 per cent of our cases, observations regarding the average age at death of patients with this disease are of great significance, particularly as regards prognosis. In a study of 1,633 patients with rheumatic heart disease, De Graff and Ling found the average age at death to be 33 years. Reid, likewise, reports an average age at death of 35.5 years and further notes that for married women with heart disease the average age at death is about five years less than for unmarried women with this disease.

When pregnancy occurs in a cardiac patient, the first and perhaps most important question to be faced is whether she will be able to go through pregnancy, labor, and the puerperium with a fair degree of safety. From an evaluation of her cardiac status, or, in other words, an estimation of the extent of cardiac damage, we are able to make a fairly accurate prognosis in the majority of cases. However, there are other factors, such as infection, which may come into play as pregnancy advances, and over which we have little or no control. In every gravid woman with cardiac disease one is faced with the question: What are the chances of this patient developing cardiac failure in pregnancy, labor, or the puerperium? A correct answer must be sought most earnestly because the maternal mortality rate in women developing congestive heart failure is many-fold that occurring in cardiac patients who do not become decompensated, either during or shortly after gestation.

The development of congestive heart failure will depend upon the degree of cardiac damage and upon certain extracardiac factors, such as upper respiratory infection and anemia.

Oppel, in a complete survey of all our patients with congestive heart failure, observed that decompensation developed in each of the last eight months of gestation as well as during the first day of the puerperium. He noted that the most frequent and important sign of heart failure during gestation is congestion of the lungs; furthermore, that age is a most valuable guide to prognosis. In 26 patients who developed congestive heart failure during pregnancy, or in labor, or in the early puerperium, Oppel found that in one-half of these cases the extent of cardiac damage was responsible for the failure in compensation, while in the other half extracardiac factors, such as upper respiratory infection, were the precipitating causes for the break. When cardiac failure did occur, its outstanding manifestation was congestion of the lungs, associated at times with hemoptysis and often progressing to pulmonary edema. The incidence of congestive heart failure in his 620 patients was only 4 per cent, a figure considerably lower than those previously reported. Oppel ascribed this low incidence to two factors, the selection of patients showing physical signs of passive congestion and the close antenatal supervision in a special cardiac clinic. He is convinced that heart failure was often prevented by careful management.

TABLE V. THE INCIDENCE OF CESAREAN SECTION IN PATIENTS WITH HEART DISEASE

|   | CLASSIFICATION |                         |                        |                         |
|---|----------------|-------------------------|------------------------|-------------------------|
|   | I              | II                      | III                    | IV                      |
| Cesarean section (cardiac indication)                 | 0              | 2                       | 5                      | 2                       |
| Cesarean section (and sterilization)                  | 0              | 2                       | 6                      | 5                       |
| Total   | 0              | 4<br>(18.1<br>per cent) | 11<br>(50<br>per cent) | 7<br>(31.8<br>per cent) |
| Total incidence of cesarean section for heart disease |                |                         | 3.26 per cent          |                         |
| Total clinic incidence of cesarean section            |                |                         | 2.2 per cent           |                         |

TABLE VI. INCIDENCE OF THERAPEUTIC ABORTION IN HEART DISEASE

|   | NUMBER OF<br>CASES | THERAPEUTIC ABORTION |          |
|---|--------------------|----------------------|----------|
|   |                    | NUMBER               | PER CENT |
| Class I   | 300                | 0                    | 0.0      |
| Class II  | 297                | 18                   | 6.0      |
| Class III   | 60                 | 13                   | 46.1     |
| Class IV  | 19                 | 6                    | 31.6     |
| Total   |                    | 37 cases             |          |
| Total incidence of therapeutic abortion for heart disease |                    | 5.4 per cent         |          |
| Total clinic incidence of therapeutic abortion            |                    | 0.79 per cent        |          |

cent. Therefore, the actual loss of fetal life because of heart disease occurred only in the group having therapeutic abortion, namely 5.4 per cent.

Prevention of conception was accomplished by tubal sterilization in a small number of patients, most of whom are in Classes III or IV. This procedure was performed at the time of section, as shown in Table V, or was effected on the third post-partum day under local anesthesia. The Madlener type of operation, or actual tubal resection, seems to give satisfactory results. Other patients in Classes II and III especially are referred to the contraceptive clinic for the necessary advice. Such is our practice, particularly if the patient has had only one child.

Mendelson and Pardee, in a recent study of the pulse and respiratory variations during labor in patients with rheumatic heart disease, found that in all their cases of intrapartum or post-partum heart failure, the pulse rate was elevated to 110 or over, either alone or with an increased respiratory rate of above 24 per minute during the first stage of labor. Furthermore, they observed no serious heart failure, irrespective of the functional classification, provided the pulse and respiration rates remained below these critical levels throughout the first stage of labor.

#### SUMMARY AND CONCLUSIONS

1. Organic heart disease is a most serious complication of pregnancy, being present in about 2 to 3 per cent of all obstetric patients and accounting for an increased maternal mortality (10.3 per 1,000), which is five times greater than that for our total obstetric patients (1.98 per 1,000).

in cases of cesarean section where a general anesthetic is contraindicated. If the latter is employed in a patient with organic heart disease, it should be, in our opinion, open drop ether or ethylene.

In our clinic, Pardee and Mendelson studied the pulse and respiratory variations in 180 normal women in labor. They found that during the first stage of labor there was little change in the pulse and respiration rates. With the onset of voluntary muscular efforts, occurring usually at or shortly before full dilatation of the cervix, these rates may or may not increase. In 10 per cent of their cases, the pulse rose to over 110 per minute after the onset of voluntary efforts, while in 19 per cent the respiratory rate exceeded 24 per minute. It is noteworthy that they were unable to correlate the pulse or respiration levels with the use of analgesia or with any particular analgesic.

TABLE IV. TYPE OF DELIVERY IN HEART DISEASE COMPLICATING PREGNANCY

| TYPE OF DELIVERY                        | CLASSIFICATION |          |     |          |     |          |     |          |
|---|----------------|----------|-----|----------|-----|----------|-----|----------|
|   | I              |          | II  |          | III |          | IV  |          |
|   | NO.            | PER CENT | NO. | PER CENT | NO. | PER CENT | NO. | PER CENT |
| Spontaneous delivery                    | 224            | 74.6     | 178 | 59.9     | 19  | 31.6     | 3   | 15.7     |
| Operative (cardiac indication)          | 12             | 4.0      | 53  | 17.8     | 21  | 35.0     | 10  | 52.6     |
| Operative other                         | 50             | 16.6     | 30  | 10.1     | 1   | 1.6      | 0   | 0.0      |
| Abortions (therapeutic and spontaneous) | 14             | 4.6      | 36  | 12.1     | 19  | 31.6     | 6   | 31.6     |
| Total                                   | 300            | 99.8     | 297 | 99.9     | 60  | 99.8     | 19  | 99.9     |

In general, the mode of delivery varied with the classification of the heart disease. For example, spontaneous delivery was permitted in about 75 per cent of the patients in Class I, whereas, only 16 per cent in Class IV delivered spontaneously. When operative delivery (for cardiac indication) is analyzed, one finds that only 4 per cent of the patients in Class I had an operative delivery, whereas, in Class IV, nearly 53 per cent had this type of delivery. The percentages for Classes II and III are found midway between Classes I and IV.

Cesarean section was performed in 3.26 per cent of the patients with heart disease as shown in Table V. Again the incidence varies with the severity of the heart lesion. For example, no sections were performed in Class I, whereas, Class III and Class IV had an incidence of 32 and 50 per cent; respectively.

Therapeutic abortion was performed in 37 patients, or 5.4 per cent, the average incidence for the clinic being only 0.79 per cent. The incidence of interrupted pregnancies varies also with the Class of heart disease from which the patient suffered as shown in Table VI. The incidence was highest in Classes III and IV, which is to be expected, and ranged from 31 to 46 per cent.

Spontaneous abortion occurred in 5.1 per cent of the patients, which is less than the clinic incidence of 6.8 per cent for spontaneous abortion. The infantile mortality was not increased in this group and was 3.84 per



stage of labor should be avoided in these patients, by forceps delivery upon full dilatation of the cervix.

9. Cesarean section has a limited, although definite, place in the treatment of heart disease in pregnancy. In our series of cases, the incidence of cesarean section on the indication of heart disease has been steadily declining during the past five years, due no doubt to improved prenatal supervision and management as well as to a definite endeavor to register the cardiac patients in the special cardiac clinic as early as possible in pregnancy.

10. Sterilization, likewise, has a proper place in the management of organic heart disease. It is our practice to effect sterilization in well over one-half of the patients in Class III who are delivered by cesarean section and in all those in Class IV.

11. The maternal mortality is about twenty-five times higher in the untreated than in the treated pregnant cardiac patient. Adequate examination and evaluation of the cardiac status at the time of the patient's first visit, proper selection of candidates for therapeutic abortion, proper prenatal care in a special cardiac clinic, sufficient bed rest and hospitalization, digitalization, and the proper method of delivery are the main factors in the treated group responsible for the low maternal death rate. Mortality from heart disease in pregnancy under such a program can be almost eliminated. In such a regimen it is essential that every cardiac patient be examined before the end of the third month of gestation when a therapeutic abortion is still feasible, should such be indicated after evaluation of the cardiac status.

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2. Rheumatic heart disease accounts for almost 95 per cent of our cardiac patients.

3. Congenital heart disease, although rare, requires careful evaluation before pregnancy is contemplated. Of these cases, those with coarctation of the aorta should be dissuaded from childbearing and, if pregnant, should have the gestation interrupted if in the first trimester; on the other hand, should the gestation be beyond the first trimester, the patient may be carried to viability or term, with delivery by cesarean section followed by tubal sterilization.

4. Congestive heart failure occurred in about 4 per cent of our cardiac patients, and was associated with a maternal mortality of 15 per cent.

5. The development of decompensation depends upon such extracardiac factors as upper respiratory infection and anemia, as well as on the degree of cardiac damage. Cardiac damage per se is responsible for about one-half the cases of congestive heart failure, while extracardiac causes account for the remainder of the cases of decompensation.

6. Proper treatment and management require:

a. Early diagnosis and proper functional evaluation. This should be done in cooperation with an internist or cardiologist.

b. Very close and frequent supervision in a special cardiac clinic or in the doctor's office.

c. The interruption of pregnancy during the first trimester in those patients with organic heart disease, in whom congestive heart failure is liable to occur should gestation proceed to term. Therapeutic abortion, on the indication of heart disease, was performed in our clinic in only Classes II to IV and amounted to about 5.4 per cent of our cardiac patients.

d. In general, no interruption of pregnancy after the fourth month.

e. Rest and varying periods of hospitalization, as indicated, prior to delivery. In general, the period or periods of hospitalization will vary with the severity of the cardiac disease or the functional classification, ranging from several days in Class I to several months in Class IV.

f. Careful consideration of the method of delivery in each instance.

g. Close scrutiny of the pulse and respiration rates during the first stage of labor. A pulse rate of over 110 per minute and a respiratory rate of over 24 per minute must be regarded as danger signals.

7. Our patients who developed cardiac failure during or shortly after labor, showed a pulse rate of over 110, alone or associated with a respiratory rate of over 24 per minute, in the *first stage* of labor. In these cases, rapid digitalization, with forceps delivery upon full dilatation of the cervix, is the treatment of choice.

8. In patients with a functional classification of Class III or IV antepartum digitalization and the relief of heart failure before the onset of labor are essential to a satisfactory outcome. In addition, the second

We believe that complete abdominal hysterectomy is little if any more time consuming than supracervical hysterectomy when a given case is not attended with untoward complicating factors. We also believe that an adequately prepared and adhered to operative plan can and does simplify the two types of operations, so that the one may be done as easily as the other. Needless to say, and this is borne out in our statistics, we do not contend that all pelvic pathology should be treated by total hysterectomy even when surgery is definitely indicated. Some pathology is grossly so overwhelming as to suggest discretion to the operator, and the few added minutes that might be required to remove a cervix in a case already potentially shocked by a prolonged procedure are not warranted. Indeed, in such fortunately rare circumstances we subscribe to the use of the supracervical operation.

Our reasons for the performance of the total operation are those brought forth by many authorities, namely:

1. That the removal of the entire organ precludes the possibility of disease in a remaining, practically useless, fragment.
2. That the cervical stump does not prevent the symptom of dyspareunia, for indeed, we do not seem to be confronted with this annoyance.
3. That the vagina, when surgery is carefully executed, is not materially shortened but rather may even be lengthened.

Before the general impression is given that our surgery is too radical let it be said that in our own minds we do not feel that such criticism is merited, particularly in view of our statistics which show that in only 45 per cent of the total hysterectomies were both adnexa removed. Actually, staff physicians train their residents in conservative gynecology.

In Table I is shown the division of the total number of cases studied and in Table II a comparison with recent figures presented by other workers.

TABLE I. DIVISION OF CASES

| TYPE OF OPERATION          | NUMBER | %     |
|----------------------------|--------|-------|
| Total hysterectomy         | 419    | 83.8  |
| Supracervical hysterectomy | 81     | 16.2  |
| Entire series              | 500    | 100.0 |

TABLE II. COMPARATIVE STATISTICS

| AUTHORS STUDIED                 | TOTAL NO. | SUBTOTAL HYSTERECTOMY | MORTALITY % | TOTAL HYSTERECTOMY | MORTALITY % |
|---------------------------------|-----------|-----------------------|-------------|--------------------|-------------|
| Harris <sup>1</sup>             | 1,145     | 314                   | 0.6         | 831                | 0.6         |
| Masson <sup>2</sup>             | 2,542     | 766                   | 0.9         | 1,776              | 1.2         |
| Miller and Prejean <sup>3</sup> | 629       | 255                   | 2.75        | 374                | 1.33        |
| Boice <sup>4</sup>              | 862       | 656                   | 3.00        | 206                | 1.00        |
| Weir <sup>5</sup>               | 1,784     | 348                   | 2.30        | 1,436              | 0.76        |
| Pearse <sup>6</sup>             | 1,616     | 1,243                 | 3.40        | 373                | 2.90        |
| Authors' series                 | 500       | 81                    | 3.70        | 419                | 1.43        |

The uncorrected mortality rate for this series was 1.80 per cent, the result of 9 deaths. This is fully explained in Table III.

# Department of Statistics\*

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## A STATISTICAL STUDY OF 500 CONSECUTIVE ABDOMINAL HYSTERECTOMIES

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SINCE the advent of a completely new regime in the department of gynecology and obstetrics at the St. Louis University group of hospitals some nine years ago, it has been our opinion that total abdominal hysterectomy is done almost to the exclusion of the supracervical operation, especially since the development of a definite operative plan.

In order to prove to ourselves that the above formulated idea was factual, we have attempted the critical study of the last 500 consecutive abdominal hysterectomies at the University hospitals.† Of these procedures, fully 80 per cent of the total operations were performed by resident gynecologists with one to two years of specialized training. Of the subtotal operations, approximately 70 per cent were done by visiting surgeons. This statement requires clarification in order to interpret properly such figures.

The greater majority of the cases presented were clinic patients. These were almost invariably operated upon by resident physicians except in those instances of extensive pathology where the member of the attending staff believed his own capabilities more suited to cope with the obstacles. By this same token, then, we can place the greater part of the mortalities under the names of fully qualified attending gynecologists, since the deaths in this series occurred most frequently in severe complicated cases. Also, carrying along on this same theme, we find a much higher mortality rate among subtotal than among total hysterectomies. This fact which, at first glance appears amazingly inconsistent, since the subtotal operation is generally regarded as technically much easier and less time consuming is, upon thorough analysis readily understood. The resident staff, together with their active preceptors, perform total hysterectomies almost routinely and, therefore, do the subtotal operation only when the condition of the patient and the pelvic and constitutional pathology warrant the less radical operation.

\*In view of the value, as matters of record, of statistical observations dealing with specific operations and procedures in institutional practice, the Editors are inaugurating this Department as a trial measure. Contributions are solicited for this purpose which shall include statistical reviews of indications, results, and other pertinent items related to the work of a particular hospital or individual in any given field.

†Werthelm operations were not included among the total hysterectomies nor were Porro operations included in the subtotal group although several of both procedures have been performed.

The morbidity figures are admittedly rather high. The number of morbid cases in the total hysterectomy group was 156, or 37.2 per cent. For the subtotal group it was 31, or 38.2 per cent. It is highly probable that these figures can and will be reduced. We believe that a more careful preoperative study and work up of patients will aid in this problem of reducing morbidity more than any other factor with the exception of the actual operative finesse and care in handling tissues that is ever the prime requisite for satisfactory surgical results. Table IV further subdivides the morbid cases.

TABLE IV. MORBIDITY

|   | TOTAL<br>HYSTERECTOMY |      | SUPRACERVICAL<br>HYSTERECTOMY |      |
|---|-----------------------|------|-------------------------------|------|
|   | NO.                   | %    | NO.                           | %    |
| 1. 100.4° F.-101.4° F. (for 2 days)                   | 22                    | 13.8 | 5                             | 16.1 |
| 2. 100.4° F.-more than 101.4° F. (for 2 days)         | 18                    | 11.5 | 4                             | 12.9 |
| 3. 100.4° F.-101.4° F. for more than 2 days           | 42                    | 26.9 | 3                             | 9.6  |
| 4. 100.4° F.-more than 101.4° F. for more than 2 days | 74                    | 47.4 | 19                            | 62.3 |

Tables V and VI require no comment. Table VII reveals the number of patients given intravenous or subcutaneous fluids in the form of glucose, blood, and saline. Several patients received more than one blood transfusion and about 33 per cent of the entire group receiving glucose or saline had such therapy employed more than once. It is

TABLE V. AGE DISTRIBUTION

|             | TOTAL<br>HYSTERECTOMY |      | SUPRACERVICAL<br>HYSTERECTOMY |      |
|-------------|-----------------------|------|-------------------------------|------|
|             | NO.                   | %    | NO.                           | %    |
| 20-30 years | 26                    | 6.2  | 10                            | 12.3 |
| 31-35 years | 64                    | 15.2 | 13                            | 16.0 |
| 36-40 years | 99                    | 23.6 | 21                            | 25.9 |
| 41-50 years | 190                   | 45.3 | 28                            | 34.5 |
| 51-60 years | 35                    | 8.3  | 9                             | 11.1 |
| 61-70 years | 5                     | 1.2  | 0                             | 0.0  |

TABLE VI. ANESTHETICS

|                  | TOTAL<br>HYSTERECTOMY |      | SUPRACERVICAL<br>HYSTERECTOMY |      |
|------------------|-----------------------|------|-------------------------------|------|
|                  | NO.                   | %    | NO.                           | %    |
| Gas-ether        | 163                   | 38.9 | 42                            | 51.8 |
| Spinal           | 162                   | 38.6 | 20                            | 24.7 |
| Ether            | 85                    | 20.2 | 19                            | 23.4 |
| Spinal and ether | 7                     | 1.6  | 0                             | 0.0  |
| Spinal and local | 2                     | 0.4  | 0                             | 0.0  |

TABLE VII. PARENTERAL FLUIDS

|                                   | TOTAL<br>HYSTERECTOMY |      | SUPRACERVICAL<br>HYSTERECTOMY |      |
|-----------------------------------|-----------------------|------|-------------------------------|------|
|                                   | NO.                   | %    | NO.                           | %    |
| Glucose and saline (I.V. or S.C.) | 179                   | 42.7 | 45                            | 55.6 |
| Blood (transfusions)              | 51                    | 12.1 | 13                            | 16.0 |

TABLE III. MORTALITY RATE

|               | TOTAL<br>HYSTERECTOMY | SUPRACERVICAL<br>HYSTERECTOMY | ENTIRE GROUP |
|---------------|-----------------------|-------------------------------|--------------|
| No. of deaths | 6                     | 3                             | 9            |
| Percentage    | 1.43                  | 3.70                          | 1.80         |

Three of the 6 deaths in the total hysterectomy group and 2 of the 3 in the subtotal group were the results of severely complicated operative cases. Only two cases, one from each group, are considered as deaths due to nonoperative causes. A brief résumé of the 9 fatalities is herewith appended:

1. Aged 37 years. Diagnosis: fibroid uterus with huge varicosities of the broad ligaments. Subtotal hysterectomy done. Spinal anesthesia. Died four hours later of shock and hemorrhage. This is, without question, an operative death due to inability to control the hemorrhage from the broad ligament varicosities.

2. Aged sixty-one years. Diagnosis: fibroid uterus. Complete hysterectomy with bilateral salpingo-oophorectomy done. Ether anesthesia. Operative time, 60 minutes. Died from evisceration, cachexia, and peritonitis on the sixteenth postoperative day.

3. Aged 60 years. Diagnosis: carcinoma of the fundus uteri and ventral hernia. Total hysterectomy and repair of hernia done. (The tubes and ovaries had been removed previously.) Ether anesthesia. Operative time, 240 minutes. Patient died from cardiac insufficiency and pneumonia on the fourth postoperative day. This death, in all probability, was due to the extremely prolonged operative procedure.

4. Aged 47 years. Diagnosis: sarcoma of the uterus. Complete hysterectomy performed. Operative time, 60 minutes. Ether anesthesia. Died suddenly on the twelfth postoperative day of pulmonary embolus.

5. Aged 59 years. Diagnosis: intraligamentary fibroid of the uterus. Operation, supracervical hysterectomy with bilateral salpingo-oophorectomy. Operative time, 60 minutes. Ether anesthesia. Patient died on the fourteenth postoperative day of arteriosclerotic heart disease and nephrosclerosis. This death was nonoperative in character.

6. Aged 59 years. Diagnosis: carcinoma of the right ovary. Complete hysterectomy and bilateral salpingo-oophorectomy done. Operative time, 80 minutes. Gas-ether anesthesia. Jejunostomy done for intestinal obstruction twenty-four days later, but the patient died six days thereafter.

7. Aged 25 years. Diagnosis: generalized abdominal tuberculosis with perforation of the colon and sarcoma of the right ovary. Total hysterectomy with bilateral salpingo-oophorectomy and resection of 4 inches of colon. Operative time, 90 minutes. Spinal and local anesthesia. The patient died of shock on the first postoperative day.

8. Aged 37 years. Diagnosis: hematometra. Supracervical hysterectomy and left salpingo-oophorectomy done together with packing of the pelvis to control hemorrhage from greatly dilated pelvic blood vessels. Operative time, 120 minutes. Spinal anesthesia. Death occurred on the day of the operation from shock and hemorrhage.

9. Aged 46 years. Diagnosis: fibroid uterus and chronic appendicitis. Operation, complete hysterectomy with appendectomy. Operative time, 60 minutes. Gas-ether anesthesia. Patient died on the third postoperative day from syphilitic aortitis, massive collapse of both lungs and arteriosclerotic heart disease. This is considered a nonoperative death.

TABLE X. OPERATIVE COMPLICATIONS

|  | TOTAL<br>HYSTERECTOMY |        | SUPRACERVICAL<br>HYSTERECTOMY |        |
|--|-----------------------|--------|-------------------------------|--------|
|  | NO.                   | DEATHS | NO.                           | DEATHS |
| Wound infections                               | 23                    | 0      | 7                             | 0      |
| Urinary infections                             | 8                     | 0      | 3                             | 0      |
| Shock  | 4                     | 1      | 2                             | 2      |
| Pelvic abscess                                 | 4                     | 0      | 0                             | 0      |
| Peritonitis                                    | 4                     | 0      | 0                             | 0      |
| Vesicovaginal fistula                          | 4                     | 0      | 0                             | 0      |
| Thrombophlebitis                               | 3                     | 0      | 2                             | 0      |
| Massive collapse of lungs and atelec-<br>tasis | 3                     | 1      | 0                             | 0      |
| Pneumonia                                      | 2                     | 0      | 0                             | 0      |
| Cardiovascular renal disease                   | 1                     | 1      | 2                             | 1      |
| Evisceration                                   | 1                     | 1      | 0                             | 0      |
| Pulmonary embolus                              | 1                     | 1      | 0                             | 0      |
| Intestinal obstruction                         | 1                     | 1      | 0                             | 0      |
| Rectovaginal fistula                           | 1                     | 0      | 0                             | 0      |
| Hemorrhage from vaginal cuff                   | 1                     | 0      | 0                             | 0      |
| Total  | 61                    | 6      | 16                            | 3      |

38.2 per cent for subtotal hysterectomy as shown fully in Table III. Doubtless the blame for a good proportion of the unexplained morbidities can be laid to a mild cystitis or pyelitis which was not diagnosed. It is practically impossible to define a subacute bladder infection unless one is constantly on guard for such a complicating factor and unless proper diagnostic measures are carried out.

TABLE XI. OPERATIVE TRAUMA

|                                | TOTAL<br>HYSTERECTOMY |        | SUPRACERVICAL<br>HYSTERECTOMY |        |
|--------------------------------|-----------------------|--------|-------------------------------|--------|
|                                | NO.                   | DEATHS | NO.                           | DEATHS |
| Rent in bladder (repaired)     | 0                     | 0      | 4                             | 0      |
| Injury to intestine (repaired) | 4                     | 0      | 0                             | 0      |

TABLE XII. PATHOLOGIC FINDINGS

| PATHOLOGY                           | NUMBER |
|-------------------------------------|--------|
| Fibromyoma of uterus                | 264    |
| Chronic pelvic inflammatory disease | 144    |
| Chronic cervicitis                  | 120    |
| Ovarian tumors                      | 91     |
| a. Benign                           | 87     |
| b. Malignant                        | 4      |
| Adenomyosis                         | 22     |
| Uterine malignancies                | 19     |
| a. Carcinoma                        | 14     |
| b. Sarcoma                          | 5      |
| Endometriosis                       | 11     |

Table XII indicates the more frequently noted pathological findings. There were, also, a myriad of other findings but these occurred rarely, as for example: hematometra, hematocervix, old ruptured ectopic pregnancy, generalized abdominal tuberculosis, carcinoma of the bladder, instrumental wound of the uterus following dilatation and curettage, etc. Chronic cervicitis was the third most frequently encountered diagnosis. This probably could have been noted at least 90 per cent of the

noteworthy that 2 or 3 residents and a like number of attending gynecologists employed intravenous glucose, 750 c.c. to 1,000 c.c. of a 10 per cent solution in saline, after almost every laparotomy. The results following this method were not perceptibly better than in those patients given parenteral fluids only when deemed necessary.

TABLE VIII. INCIDENTAL DATA

|                                       | TOTAL<br>HYSTERECTOMY | SUPRACERVICAL<br>HYSTERECTOMY |
|---------------------------------------|-----------------------|-------------------------------|
| Average hospital stay (postoperative) | 14.82 days            | 15.40 days                    |
| Average time of operations            | 83.90 minutes         | 84.56 minutes                 |

Table VIII furnishes data on the average postoperative hospital stay and the average duration of the operations from incision to skin closure. Needless to say the operative time is increased by the amount and degree of the pathology encountered. However, the personal surgical skill of various operators did not play a major role in the time consumption in these cases. Fifty to sixty minutes usually sufficed to complete a moderately uncomplicated total hysterectomy when done by the resident staff.

TABLE IX. OPERATIVE PROCEDURES

|  | TOTAL<br>HYSTERECTOMY | SUPRACERVICAL<br>HYSTERECTOMY |
|--|-----------------------|-------------------------------|
| <i>Hysterectomy:</i>   |                       |                               |
| With bilateral salpingo-oophorectomy   | 131                   | 21                            |
| With no other procedures   | 92                    | 23                            |
| With unilateral salpingo-oophorectomy  | 58                    | 13                            |
| With adhesiolysis and bilateral salpingo-oophorectomy                        | 31                    | 0                             |
| With appendectomy  | 18                    | 7                             |
| With adhesiolysis and unilateral salpingo-oophorectomy                       | 15                    | 4                             |
| With appendectomy and unilateral salpingo-oophorectomy                       | 14                    | 1                             |
| With perineorrhaphy and bilateral salpingo-oophorectomy                      | 11                    | 0                             |
| With appendectomy and bilateral salpingo-oophorectomy                        | 10                    | 3                             |
| With adhesiolysis  | 9                     | 2                             |
| With closure of cervix and bilateral salpingo-oophorectomy                   | 8                     | 0                             |
| With repair of hernia and bilateral salpingo-oophorectomy                    | 7                     | 1                             |
| With perineorrhaphy  | 6                     | 0                             |
| With repair of intestine and bilateral salpingo-oophorectomy                 | 5                     | 0                             |
| With adhesiolysis, repair of hernia and unilateral salpingo-oophorectomy     | 2                     | 0                             |
| With anterior and posterior colporrhaphy and bilateral salpingo-oophorectomy | 1                     | 0                             |
| With cecostomy, repair of rectum and bilateral salpingo-oophorectomy         | 1                     | 0                             |
| With repair of bladder   | 0                     | 4                             |
| With repair of intestine   | 0                     | 1                             |
| With packing of pelvis   | 0                     | 1                             |

Table X reveals the complications that occurred while the patients were hospitalized. These, although numerous, do not entirely account for the morbidity figures of 37.2 per cent for total hysterectomy and



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## Correspondence

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### Thyroid Extract and Iodine Therapy in Pregnancy Toxemia

To the Editor:

I have read with interest Dr. Colvin's article on this subject in the February, 1942, issue of the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY*. There are several points upon which I would like to have clarification or make comments.

In Tables IV and V it is shown that in the two control groups of mild vascular disease (untreated), the incidence of toxemia was 14.6 and 6.1 per cent, respectively. If there can be such a great difference in the incidence of toxemia in two control groups, can the difference in the incidence of toxemia between treated and untreated cases be considered of significance?

The author does not indicate whether or not the period of observation was the same for all cases, or whether the period of treatment was comparable for all of the treated groups. No mention is made of the other forms of treatment, such as bed rest, diet, etc., that may have been recommended for the control or treated groups. These might have an important bearing on the conclusions.

There are two statements in the article that seem to be contradictory. "For some unaccountable reason, the administration of iodine to cases of vascular disease during pregnancy fails to lower the already low incidence of toxemia in these cases;" "The results indicate that the incidence of toxemia superimposed on early vascular disease is reduced 50 per cent by the use of iodine."

Table III shows 396 "normal" cases with minus basal metabolism, in the text is a statement that only those with a minus metabolism were treated, yet Table VIII shows only 273 "normal" cases received treatment. The author does not explain why the 123 remaining patients with minus basal metabolism were not treated. There are 143 "normal" cases in Table III with basal metabolic rates of 0 or plus. Presumably these would be the "normal" cases for control, yet Table VIII lists 316 "normal" control cases.

The author has made an extremely interesting study, but the evidence presented does not seem to this reader to substantiate the conclusions.

EDWIN F. DAILY, M.D.,  
*Director, Division of Health Services,  
Federal Children's Bureau.*

June 24, 1942.

### Reply by Dr. Colvin

To the Editor:

It happens too often in medical literature that tables, and conclusions drawn from them, are accepted as facts without a searching analysis being made by the reader. We are indebted to Dr. Daily for the questions and criticisms offered relative to our article.

time, but we included only those cases presenting gross pathologic changes in the cervix. The pathology noted did not differ greatly from that reported in similar articles with fibromyomas of the uterus and chronic pelvic inflammation being very frequent.

TABLE XIII. POSTOPERATIVE EXAMINATIONS

| FINDINGS                  | TOTAL<br>HYSTERECTOMY | SUPRACERVICAL<br>HYSTERECTOMY |
|---------------------------|-----------------------|-------------------------------|
| Vaginal cuff granulations | 56                    | 0                             |
| Menopausal syndrome       | 48                    | 7                             |
| Wound infections          | 19                    | 6                             |
| Shortened vagina          | 9                     | 0                             |
| Hernias                   | 4                     | 1                             |
| Rectovaginal fistula      | 4                     | 0                             |
| Vesicovaginal fistula     | 3                     | 0                             |
| Pelvic abscess            | 3                     | 0                             |
| Senile vaginitis          | 2                     | 0                             |
| Dyspareunia               | 1                     | 0                             |
| Frigidity                 | 1                     | 0                             |
| Carcinoma of the rectum   | 1                     | 0                             |
| Thrombophlebitis          | 0                     | 4                             |
| Cervical erosion          | 0                     | 2                             |
| Carcinoma of cervix       | 0                     | 1                             |
| Totals                    | 151                   | 21                            |

Regarding Table XIII, we have not included cases that were symptom-free on the first postoperative examination. Two hundred and sixty-two complete hysterectomies and 57 supracervical hysterectomies were apparently completely cured at the time of the first examination which usually took place six weeks after operation. There were 9 cases in which the vagina was considered to be shortened after complete hysterectomy. However, of these only 2 revealed a total length of less than 3 inches. The other 7 patients had vaginas ranging from 3 to  $3\frac{1}{4}$  inches in length. Vaginal cuff granulations, the most frequent finding, were usually slight in degree and readily responded to therapy with caustics. Seldom did these granulations persist after 1 or 2 applications of 2 to 10 per cent silver nitrate solution.

In conclusion, we fully realize that reports of this nature have been numerous in the literature. As previously implied, we embarked upon this study for our own enlightenment and the results are, we feel, gratifying. Each case in this series was personally fully studied by us and the statistics presented are accurate as taken from the records of Firmin Desloge Hospital.

Since a large proportion of the total hysterectomies were performed by resident gynecologists with a minimum of training, and since the mortality figure of 1.43 per cent for these cases is low, we firmly believe that a given physician may be as facily trained in the performance of total abdominal hysterectomy as in the supracervical operation and that this physician will be quite competent to perform the more radical procedure. We do not deem it necessary to campaign for the routine use of the total operation since this has been advocated for years. A definite, planned, operative technique can, with practice, give most excellent results whether that technique be directed toward the performance of total or subtotal hysterectomy.

We wish to express our deep appreciation to Dr. William H. Vogt, Sr., Director of the Department of Gynecology and Obstetrics, who has personally supervised not only a large number of these operations but also the composition of this paper.

## Editorial

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### Women in the War Effort

THE present global conflict has called into action the participation of women to a degree as never before. Not only industry but what might be designated as the supplementary combat forces have drawn upon the ranks of those who can no longer be regarded in a popular sense as the weaker sex. To make woman's participation effective as a war worker, her essentially feminine characteristics have had to be taken into account and special rules and regulations devised to protect her in the hazards of her new activities. Government and medical organizations have combined in the effort to preserve her health and well-being during a period of stress in which it has been assumed she might prove physically inferior.

Recent promulgations from official sources indicate a necessity for this enlistment of women in the war industries. The results of their labors seem to have proved of great value and their induction into factory and similar employment is believed to release many men for the combat forces. If this constitutes a part of the necessary effort to win the war, we should accept it. In doing so, however, we must divorce from the movement any possible underlying element of glamor and choose as participants those women whose entrance into labor would not disrupt their obligations toward society and the family.

Admittedly there are hazards associated with factory work which involve men less than they do women, therefore the conditions for employment of the latter must be worked out even more carefully. The ordinary requirements of general physical and mental soundness as we might term them, must be supplemented by those involved with the genital sphere. If disturbances in the latter would incapacitate or endanger or complicate employment, they must be sought out and treated. In addition, however, there are obligations to a family and small children which cannot be set aside for the mere desire to increase an income. If these obligations are overcome by providing accessory services for the purpose, will they not prove both costly and unsatisfactory in more than one sense? In addition there is the plan for providing for the special care of pregnant women in factory jobs. As a matter of fact why should pregnant women be employed at all in hazardous occupations or any others that make demands on physical resources which should be devoted to carrying out her foremost obligation to society? For years we have been developing methods to protect her during this all-important period, and now we are urging

First of all, we admitted in the paper (page 190) that, "it would have been desirable had the study covered a larger series of cases in both the thyroid and iodine treated groups, but the benefit of iodine in reducing the incidence of toxemia is so striking that we feel that a larger series of cases would not materially alter the results." Also on page 191, we expressly worded the final conclusion "*gives promise of effecting a great reduction in the frequency of true toxemia of pregnancy,*" to encourage further trial of the treatment. We did not wish to imply that iodine had as yet been proved to be a specific prophylactic agent for toxemia of pregnancy.

In his comment relative to Tables IV and V, a variation of 14.6 per cent and 6.1 per cent in the control groups of 48 and 49 cases, can easily occur with a small number of cases, whereas the percentages based upon 155 and 161 cases are more reliable.

The manner of treatment and period of observation were comparable for all the treated and control groups, and we do not believe these factors have any bearing on the conclusions.

Concerning the two apparently contradictory statements referred to by Dr. Daily: If we add the nontreated mild vascular disease cases in Table IV (48) and Table V (49), we obtain 97 cases, as given in Table VII, with 10 cases of toxemia or 10.3 per cent, which is a more reliable figure. Since the iodine treated vascular disease cases (39) showed toxemia in only 5.1 per cent, our statement that "the incidence of toxemia superimposed on vascular disease is reduced 50 per cent by the use of iodine," is the correct one, rather than our statement "for some unaccountable reason the administration of iodine to cases of vascular disease during pregnancy fails to lower the already low incidence of toxemia in these cases."

His question in regard to Tables III and VIII apparently arises from the fact that he interprets normal cases as those showing plus metabolic rates, whereas we designate normal cases as those free from vascular disease.

It is our intention to bring this investigation up to date at some future time by the addition of several hundred additional cases.

E. D. COLVIN, M.D.

Atlanta, Ga., July 6, 1942.

# Society Transactions

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## SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

*ANNUAL MEETING AT ATLANTA, GA., FEBRUARY 6 AND 7, 1942*

The following papers were presented:

- Stricture of the Ureter in the Female.** A. J. Kelly, Savannah, Ga.
- Vitamin Studies in Vulvar Dermatoses.** Robert Greenblatt, Augusta, Ga.
- Detailed Technique of a Modified Local Anesthesia for Cesarean Section.** Alfred C. Beck, Brooklyn, N. Y. (by invitation). (For original article, see page 558.)
- Eclampsia and Ovarian Pregnancy.** C. B. Pride, Morgantown, W. Va., and M. Pierce Rucker, Richmond, Va. (For original article, see page 575.)
- Placental Polyp with Severe Late Puerperal Hemorrhage.** Charles W. Dorsey, Roanoke, Va. (For original article, see page 591.)
- Anencephalus (with Acute Hydramnios) Diagnosed by X-ray.** Waverly R. Payne, and Harvey G. Bland, Newport News, Va. (For original article, see page 593.)
- Acute Yellow Atrophy of the Liver.** C. H. Mauzy, Winston-Salem, N. C.
- Unusual Gynecologic-Obstetric History.** Robert Seibels, Columbia, S. C.
- Diaphragmatic Hernia as a Complication of Pregnancy.** A. M. Groseclose, Roanoke, Va.
- Puerperal Uterine Contractions.** William Bickers, Richmond, Va. (For original article, see page 581.)
- Comparative Measurements of the Female Pelvis.** Kenneth Dickinson and I. M. Procter, Raleigh, N. C. (For original article, see page 585.)
- The Etiologic and Pathologic Factors in a Series of 1741 Fibromyomas of the Uterus.** Richard Torpin, Edgar Pund, and W. J. Peeples, Augusta, Ga. (For original article, see page 569.)
- Utopian Obstetrics—President's Address.** R. A. Bartholomew, Atlanta, Ga. (For original article, see page 553.)

her to expose herself to a possible interruption of her child-bearing function. Surely the supply of female labor can be augmented from other available sources, among which is that army of young women engaged in non-essential occupations, including those catering to vanities, fashions, and amusements. A greater effort to obtain recruits from such sources should be developed before invading the ranks of pregnant women to fill a possible gap. The responsibilities and strains of a factory job in a war industry should not become involved with thoughts centered on small children left at home or elsewhere, or about the outcome of a pregnancy.

This war is defined as a total war. Consequently it involves every one, perhaps indiscriminately, including men, women, and children. In our efforts, however, to bring it to a successful conclusion, we must weigh carefully what each group can do to achieve that end and in the meanwhile to preserve, so far as woman is concerned, her particular function in our social economy. This applies above all to her place as a prospective mother. *Pregnancy may eventually prove more worth while than making bullets.* Whatever problems may be involved, they demand attention and the possible solution must be based on reasoned study and not hysteria. Physically fit women, married or unmarried, and free from family ties, should, in our vast population, be found in sufficient number to rule out a resort to pregnant women in our expanded program of war industry.

Flexner, Louis B., and Gellhorn, Alfred: *A Comparative Study of Placental Permeability*, *Anat. Rec.* 82: 411, 1942.

This study attempted to show a difference in permeability of morphologically different placentas as measured by the rate of transfer of radioactive sodium. Dividing various mammalian placentas into types, according to the numbers of layers of tissue interspersed between maternal and fetal blood, the authors were able to show an inverse correlation to the rate of transfer.

L. M. HELLMAN

Winkler, H., and Linden, L.: *The Change in the Treatment of Placenta Previa During the Last Forty Years*, *München. med. Wchnschr.* 88: 66, 1941.

Winkler and Linden analyzed the results of 373 cases of placenta previa observed from 1900 to 1939 in 21,724 labor cases. This represents an incidence of 1.72 per cent. The complications generally observed in cases of placenta previa were hemorrhage before and during labor, malpresentation of the fetus, atony of the uterus and post-partum hemorrhage. In this series of cases, delivery was accomplished by abdominal cesarean section in 22 per cent, by spontaneous delivery in 20.6 per cent, Braxton Hicks' version in 18.8 per cent, the use of a bag and Braxton Hicks' version in 14 per cent, and spontaneous delivery after a bag in 7.5 per cent.

In recent years the tendency has been to perform more abdominal cesarean sections in cases of placenta previa, because this operation yields the best results for both mother and child.

J. P. GREENHILL

Rustia, Guillermo, and Tancinco, Gloria: *Placenta Previa: Analysis of 369 Cases*, *J. Philippine Islands M. A.* 20: 649, 1940.

An analysis of 369 cases of placenta previa is presented with regard to the frequency, the maternal morbidity and mortality, the fetal mortality and the results obtained. There were in all 16 deaths in the series, a percentage of 4.33. Two women died before delivery, five died of puerperal infection, and nine died a few hours after delivery either from acute anemia or shock. Spontaneous delivery occurred in 124 cases in this series. Operative delivery was performed in the other cases.

The following tabular statement shows the results obtained: The Willet's method of operation was performed 61 times:

|                             |    |                |
|-----------------------------|----|----------------|
| No. of mothers who survived | 60 | 98.36 per cent |
| No. of mothers who died     | 1  | 1.63 per cent  |
| No. of children living      | 19 | 31.14 per cent |

The Braxton Hicks' version was performed 62 times:

|                             |    |                |
|-----------------------------|----|----------------|
| No. of mothers who survived | 58 | 93.54 per cent |
| No. of mothers who died     | 4  | 6.45 per cent  |
| No. of children living      | 0  | 0.00 per cent  |

Cesarean section was performed 73 times:

|                             |    |                |
|-----------------------------|----|----------------|
| No. of mothers who survived | 71 | 97.39 per cent |
| No. of mothers who died     | 2  | 2.73 per cent  |
| No. of children living      | 49 | 67.12 per cent |

The Braxton Hicks' version is rapidly losing popularity in most clinics. The technical difficulties of the procedure limit its use to trained obstetricians. The Willet's method, as well as cesarean section, has its own place in the management of placenta previa.

C. O. MALAND

# Department of Reviews and Abstracts

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## Selected Abstracts

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### Placenta

Rauramo, N., and Kahanpaa, V.: The Principal Methods of Treating Cases of Uteroplacental Apoplexy, *Acta obst. & gynec. Scandinav.* 20: 243, 1940.

The authors collected 163 cases of uteroplacental apoplexy observed at the Women's Clinic in Viipuri. These constituted an incidence of 0.7 per cent of the 22,058 obstetric cases seen at this clinic. The cases were divided into those treated obstetrically and those treated surgically. Before 1934 the treatment was conservative but following that year in an effort to improve the prognosis of the babies, the surgical line of treatment was instituted.

Among the 94 women treated conservatively, 76 per cent had spontaneous deliveries and only three had cesarean sections. Among the 69 women treated surgically, spontaneous deliveries occurred in 34 per cent and 47 per cent had cesarean sections. Vaginal operations were performed in 21 and 19 per cent, respectively. There were six deaths, of which five were in the conservative group and one in the surgical, but all of these six patients were delivered through the vagina. Four of the six women showed evidences of severe renal disease. A change in the treatment from a conservative one to a surgical one reduced the mortality of the children from 52 to 37 per cent.

Uteroplacental apoplexy is not considered as a pregnancy toxemia but indicates severe vascular changes occurring in cases of toxemia. In fatal cases, the cause of death might be hemorrhage but not a severe toxemia. Hence, the more severe cases are not suitable for cesarean section.

A follow-up was made by the author who found that uteroplacental apoplexy does not lead to sterility.

J. P. GREENHILL

Ballin, R.: Premature Separation of the Placenta, *Monatschr. f. Geburtsh u. Gynäk.* 112: 257, 1941.

Whereas, formerly, mechanical trauma and inflammation of the endometrium were considered to be the pathologic factors in abruptio placentae, Ballin maintains that neuropathy or blood pressure variations of unknown causes are now believed to be the chief causes of premature detachment of the placenta. In the author's series the maternal mortality was 7 per cent, but a number of women were brought to his hospital in a moribund condition. The infant mortality was 59 per cent, of which 50 per cent were either too premature to live or were already dead in utero.

J. P. GREENHILL



was 87.5 per cent in patients not operated upon and 57 per cent in those patients operated upon. This grave complication of pregnancy according to the author should be treated only by surgery.

MARIO A. CASTALLO

Dippel, A. Louis, and Brown, Webster H.: *Direct Visualization of the Placenta by Soft-Tissue Roentgenography*, New England J. Med. 223: 316, 1940.

The authors discuss the various methods by which the placenta can be visualized and describe in detail the special usefulness of soft-tissue roentgenography. It represents a valuable aid in cases of suspected placenta previa and usually obviates the necessity of vaginal examination. The paper includes six excellent roentgenograms.

HUGO EHRENFEST

Crainicianu, A.: *The Early Diagnosis of Pregnancy by the Friedman-Brouha Reaction, Aided by Transperitoneal Ovarioscopy*, Rev. franç. de gynéc. et d'obst. 35: 30, 1940.

At the present time there are 48 tests to determine early pregnancy, but those generally employed are the Aschheim-Zondek on the mouse and the Friedman-Brouha tests on the rabbit. Both of these tests when properly performed are practically 100 per cent correct. The Friedman test is more popular because the results may be obtained in forty-eight hours. In order to diminish even this time, the author introduced the use of transperitoneal ovarioscopy. The principle of this procedure consists of examining the ovaries through a ureteroscope from time to time to determine the first modifications of the Graafian follicles. The aim is to detect infrafollicular hemorrhage which is the characteristic of a positive pregnancy reaction. The author used this method in 100 cases of suspected pregnancy, of which 50 were positive. A positive reaction was recognized by this procedure in less than twenty-four hours in 80 per cent of the cases. In negative cases the ovarioscopic examinations were continued at intervals up to forty-eight hours.

J. P. GREENHILL

Scott, William A.: *The Treatment of Placenta Previa*, Canad. M. A. J. 42: 442, 1940.

The author analyzed a series of 81 patients with placenta previa at the Toronto General Hospital. Of these, 17 were complete and 64 incomplete. Two maternal deaths occurred. The fetal mortality rate was 40 per cent which, when reduced by nonviable, macerated, and deformed fetuses became 28.4 per cent. He emphasizes that all cases should be treated in the hospital and that many of the emergencies could be avoided if the significance of the first bleeding was appreciated. Cesarean section should not be routine but is the safest method in nearly all cases of complete placenta previa. The hydrostatic bag has a place in the management of properly selected cases. Version is a valuable method of treatment for emergency cases which may have to be treated in the home.

CARL P. HUBER

Caldera, R.: *Placenta Previa. A Review of 251 Cases*, J. Obst. & Gynaec., Brit. Emp. 46: 531, 1939.

Caldera reports 251 cases of placenta previa in 26,116 labors, an incidence of one in 104 labors.

During the last four years there were 199 cases of placenta previa with 23 deaths, giving a maternal mortality of 11.5 per cent.

Vaughn, Charles E., Weaver, R. T., and Adamson, D. L.: Roentgenographic Visualization of the Placenta, Utilizing the Plastic Filter, *Canad. M. A. J.* 46: 314, 1942.

A brief history of placentography is given. The technical difficulties of adequate visualization are pointed out, and use of a graded plastic opaque screen described. The grading of the screen is such that, in the lateral view, more x-rays are allowed to pass through the region of the spine and pelvis than through the anterior abdomen. The results in 52 cases are excellent. Not only the anterior and posterior walls of the uterus are well visualized, but also the lower uterine segment.

J. M. HELLMAN

Sala, Silvestre L., and Bergdolt, Enrique G.: New Observations on the Diagnosis of Placenta Previa by Cystography, *Arch. de la clin. obst. y Ginec. "Eliseo Canton"* 1: 164, 1942.

Sala and Bergdolt have found that 25 c.c. of a 12.5 per cent solution of NaI introduced into the bladder produces a better radiogram than the 40 c.c. previously used. With the patient supine the x-rays are directed ventrodorsally; at the midpoint of the pubumbilical line; 3 sec. exposure, focal distance 76 cm., 65 kv. and 100 ma. Variations in technique such as the use of air as contrast medium and different angles of incidence of the rays have not increased the efficiency of the procedure. Normally in the eighth and ninth months of gestation, the shadows of the fetal head and the filled bladder are contiguous, although a separation up to 1 cm. is perfectly normal. The presence of the placenta between the fetal head and the shadow of the bladder causes an increase in this space. Earlier, in the seventh month, the separation in some normal cases is greater than 1 cm.

The most important causes of error in diagnosis are: opacities in the rectum, polyhydramnios and lateral flexion of the uterus, prolapse or shortness of the cord, low lying tumors, narrow pelvis and, particularly, a low lying placenta on the posterior wall of the uterus. Another important source of error may occur in cases of premature separation of the placenta when clots accumulate in the lower uterine segment.

In the 21 cases presented, the authors claim 90.5 per cent accurate diagnoses. In one of the two cases incorrectly diagnosed as placenta previa, the radiogram showed a triangular area of separation between the fetal head and the bladder, with the apex at the midline and the base toward the left at which point the separation was 21 mm. At delivery large clots were passed immediately after the fetus and before the placenta, indicating a premature separation of the placenta and probable presence of a clot in the position of the clear space in the radiogram. The second case in error was that of a patient with a generally contracted pelvis of mild degree.

The authors believe that experience permits recognition of certain causes of error before making the radiographic diagnosis and that the method can be very useful in clinical practice.

J. P. GREENHILL

Jakob, Alfredo: Placenta Accreta, Imminent Rupture Gravid Uterus, *Bul. Soc. de obst. y ginec. de Buenos Aires* 19: 488, 1940.

The author reviews the literature. All of the authors are of the opinion that in a previous history one finds a history of puerperal infection or curettage. In rupture of the uterus in placenta accreta, this association was verified thirteen times, and in this group eight deaths occurred. During pregnancy the symptomatology is vague. Certain pregnant women have pain, others might have slight bleeding. Mortality

The women in this series were discharged from the hospital as early as women who had normal labors provided they were not too anemic. The author advises the intra-gluteal administration of prontosil immediately after delivery to all women in whom there is likelihood that infection will set in after labor. In addition prontosil tablets should be given during the first four days.

J. P. GREENHILL

**Browne, F. J.:** Danger of Willett's Forceps in Placenta Previa, *Proc. Roy. Soc. Med.* 32: 1209, 1939.

Since its first description, in 1925, the Willett forceps has been used in 252 instances among 3,103 cases of placenta previa in 11 teaching hospitals of Great Britain. Maternal mortality amounted to 3.5 per cent and fetal mortality to 46.4 per cent. The forceps inevitably produces a more or less lacerated wound on the fetal scalp which may become infected by vaginal bacteria. The likelihood of infection is increased by death of the fetus and delay of delivery after application of the forceps—two unfavorable conditions often present in placenta previa cases.

The author reports two observations of Welch bacillus infection following the use of the Willett forceps.

HUGO EHRENFEST

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## Item

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### American Board of Obstetrics and Gynecology

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Saturday, February 13, 1943, at 2 P.M. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination held later in the year. All applications must be in the office of the Secretary by November 16, 1942.

Effective this year there will be only one general classification of candidates, all now being required to have been out of medical school not less than eight years, having in that time completed an approved one year general rotating internship and at least three years of approved special formal training, or its equivalent, in the seven years following the interne year. This Board's requirements for internships and special training are similar to those of the American Medical Association since the Board and the A. M. A. are at present cooperating in a survey of acceptable institutions. All candidates must be full citizens of the United States or Canada before being eligible for admission to examinations.

All candidates will be required to take the Part I examination, which consists of a written examination and the submission of twenty-five (25) case history abstracts, and the Part II examination (oral-clinical and pathology examination). The Part I examination will be arranged so that the candidate may take it at or near his place of residence, while the Part II examination will be held late in May, 1943, in that city nearest to the largest group of applicants. Time and place of this latter will be announced later.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

Of the 23 deaths, 11 occurred before delivery; in 6 of these, death could be attributed solely to hemorrhage, while in the remaining five cases shock following podalic version was an important contributory factor. In the case of the 12 patients whose deaths occurred after delivery, 3 were due to puerperal sepsis; with regard to the remaining 9, shock following podalic version in 8 cases and delivery by the forceps in one case were responsible for the fatal issue. Thus in no less than 20 cases the cause of death was hemorrhage complicated by shock.

In a country like Ceylon, where malaria and ankylostomiasis are endemic, the majority of patients are anemic and ill-nourished, and in such patients even a small hemorrhage may lead to serious results. Moreover, many patients seek hospital treatment after they have had repeated hemorrhages.

The percentage of stillbirths for the central, marginal, and lateral varieties is 69.6, 49.4, and 45, respectively.

Podalic version was the method of treatment adopted in 87 cases. The maternal mortality was 17.2 per cent and the fetal mortality 74 per cent. In 13 cases of breech presentation when a leg was brought down, the maternal mortality was 7.7 per cent and fetal mortality 69.2 per cent.

Cesarean section is the safest method of delivery for both the mother and the child. Only 5 patients were treated by this method, with no maternal nor fetal deaths. The membranes were ruptured artificially on 38 occasions. There were no maternal deaths and the fetal mortality was 39.4 per cent.

J. P. GREENHILL

Fleming, John G.: Premature Separation of the Normally Implanted Placenta. A Study of 72 Cases, *J. Medicine* 20: 271, 1939.

A study of 72 cases of premature separation of the normally implanted placenta revealed (University of Cincinnati) an incidence of separation of 1 in 57.5 cases in the general deliveries, and of 1 in 14 cases in the special toxic-hypertensive-nephritic syndrome. Within this toxic group of cases, separation occurred four times as often as in the general deliveries, and one and one-half times as often as eclampsia.

Toxemia was a complication in 48, or 66.6 per cent, of the cases. Some aspect of the toxic-hypertensive state, often of a severe degree, was present in the majority of the cases complicated by internal hemorrhage and of those resulting in fetal and maternal deaths.

The high incidence of the condition in youthful patients of low parity may possibly indicate a predisposition in certain individuals to the toxic-hypertensive-vascular disease process. This predisposition may also account for the frequent association of the more severe cases with repeated pregnancies and advancing years.

There is considerable evidence that, in the majority of cases, a general vascular or arteriolar spastic damage, now recognized as the pathologic process underlying the toxic and eclamptic states, is also active in the uterus in infarction of the placenta and in partial and complicated separation of the placenta.

Three maternal deaths and 29 fetal deaths, a rate of 4.2 and 40.3 per cent, respectively, followed delivery of six patients from above and 66 from below. Conservative management results in one maternal death, a rate of 1.5 per cent in the 66 patients delivered from below.

J. P. GREENHILL

Pohl, A.: What Value Has the Prophylactic Administration of Prontosil in Cases of Manual Removal of the Placenta, *Med. Klin.* 35: 346, 1939.

In a series of 46 cases of manual removal of the placenta, the author found that the prophylactic use of prontosil prevented serious infection in the puerperium.

- New Orleans Obstetrical and Gynecological Society.** *President*, E. L. Zander. *Secretary*, Eugene Countiss, 921 Canal St., New Orleans, La. Meetings held every other month.
- St. Louis Gynecological Society.** *President*, S. A. Weintraub. *Secretary*, Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** *President*, T. Henshaw Kelly. *Secretary*, R. Glenn Craig, 490 Post Street, San Francisco, Calif. Regular meetings held second Friday in month, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** *President*, Roy Grogan. *Secretary*, J. McIver, 714 Medical Arts Building, Dallas, Texas.
- Michigan Society of Obstetricians and Gynecologists** (formerly the Detroit Obstetrical and Gynecological Society). *President*, H. C. Walser. *Secretary*, Harold C. Mack, 955 Fischer Bldg., Detroit, Mich. Meeting first Tuesday of each month from October to May (inclusive).
- Obstetric Society of Syracuse Hospitals.** *President*, Edward C. Hughes. *Secretary*, Nathan N. Cohen, 713 East Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists.** *President*, T. M. Boulware, Birmingham, Ala. *Secretary*, Eva F. Dodge, Montgomery, Ala. Next meeting Montgomery, Ala., April, 1942.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Texas. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society.** *President*, Glen N. Rotten. *Secretary*, R. Philip Smith, 1305 Fourth Avenue. Meetings third Wednesday.
- Denver Obstetrical and Gynecological Society.** *Secretary*, Emmett A. Mechler, 1612 Tremont St., Denver, Colo.
- Wisconsin Society of Obstetrics and Gynecology.** *President*, Roland S. Cron. *Secretary*, Robert E. McDonald, 425 E. Wisconsin Ave., Milwaukee, Wis. Meetings held in May and October.

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## Books Received

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**PRINCIPLES OF EXTRAPERITONEAL CAESAREAN SECTION.** By James V. Ricci, M.D., Associate Clinical Professor of Gynaecology and Obstetrics, New York Medical College, etc., and James Pratt Marr, M.D., Associate Attending Surgeon, Women's Hospital in the State of New York, etc. 47 illustrations, 224 pages. Blakiston Company, Philadelphia, 1942.

**SEROLOGY IN SYPHILIS CONTROL.** With an Appendix for Health Officers and Industrial Physicians. By Reuben L. Kahn, M.S., D.Sc., Director of Clinical Laboratories and of Serologic Consultation Service of University of Michigan Hospital, etc. 206 pages. The Williams & Wilkins Company, Baltimore, 1942.

**ENDOCRINOLOGY.** Clinical Application and Treatment. By August A. Werner, M.D., Assistant Professor of Internal Medicine, St. Louis University School of Medicine, etc. Second edition, thoroughly revised. Illustrated with 327 engravings and a colored plate. 924 pages. Lea & Febiger, Philadelphia, 1942.

**LEADERS OF MEDICINE.** Biographical Sketches of Outstanding American and European Physicians. By Solomon R. Kagan, M.D. 176 pages, four illustrations. The Medico-Historical Press, Boston, Mass., 1941.

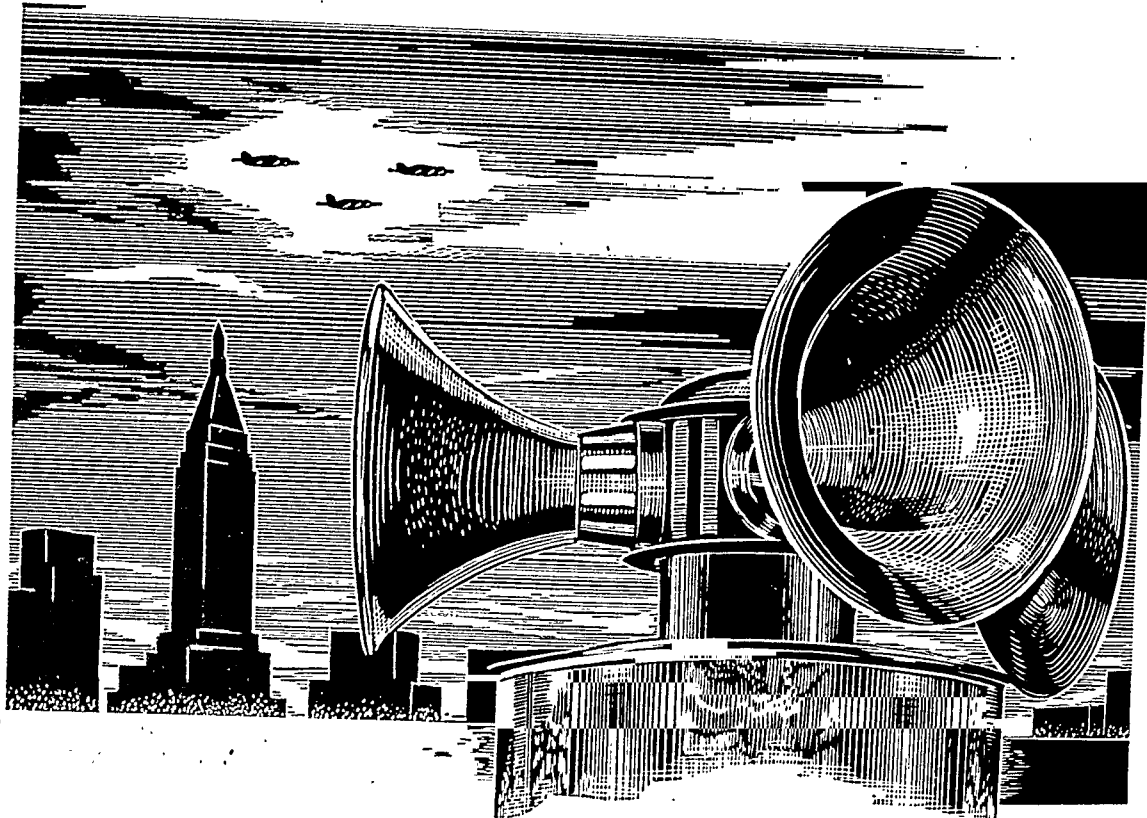
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TABLE OF CONTENTS ON PAGE 6

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## CONTENTS FOR NOVEMBER, 1942

### AMERICAN GYNECOLOGICAL SOCIETY

SIXTY-SEVENTH ANNUAL MEETING, JUNE 15 TO 17, 1942

|   |     |
|---|-----|
| Presidential Address. W. C. Danforth, M.D., Evanston, Ill. ....   | 743 |
| Studies on Head Molding During Labor. Howard C. Moloy, M.D.,<br>M.S.C., New York, N. Y. ....  | 762 |
| Classification of the Obstetric Pelvis Based on Size, Mensuration, and<br>Morphology. Kyle B. Steele, M.D., and Carl T. Javert, M.D.,<br>New York, N. Y. .... | 783 |
| Observations of the Development of Pelvic Conformation. Daniel G.<br>Morton, M.D., San Francisco, Calif. ....   | 799 |
| Solution of Posterior Pituitary Sulfonate (Pit-Sulfonate) in Labor.<br>William J. Dieckmann, M.D., and Morris S. Kharasch, Ph.D.,<br>Chicago, Ill. ....       | 820 |
| Intestinal Injuries Resulting from Irradiation Treatment of Uterine<br>Carcinoma. Albert H. Aldridge, B.S., M.D., F.A.C.S., New York,<br>N. Y. ....           | 833 |
| Hormonal Influences Upon the Ureter. J. Mason Hundley, Jr., M.D.,<br>William K. Diehl, M.D., and Everett S. Diggs, M.D., Baltimore,<br>Md. ....               | 858 |
| The Surgical Treatment and Postoperative Care of Vesicovaginal<br>Fistula. Norman F. Miller, M.D., Ann Arbor, Mich. ....                                      | 873 |
| Partial Colpocleisis as an Approach to Vesicovaginal Fistula Following<br>Total Hysterectomy. Frederick C. Holden, M.D., New York,<br>N. Y. ....              | 880 |
| Morphine Sulfate as an Obstetric Analgesic. William F. Mengert,<br>M.D., Iowa City, Iowa ....   | 888 |

### Special Article

|   |     |
|---|-----|
| Gynecologic and Other Implications Which Relate to an Ageing Female<br>Population. George W. Kosmak, A.B., M.D., New York, N. Y. .... | 897 |
|---|-----|

### Department of Reviews and Abstracts

|  |     |
|--|-----|
| Selected Abstracts—Endocrinology ..... | 911 |
|--|-----|

### Correspondence

|                      |     |
|----------------------|-----|
| Correspondence ..... | 920 |
|----------------------|-----|

### Announcement

|                                   |     |
|-----------------------------------|-----|
| A Registry of Ovarian Tumors..... | 922 |
|-----------------------------------|-----|

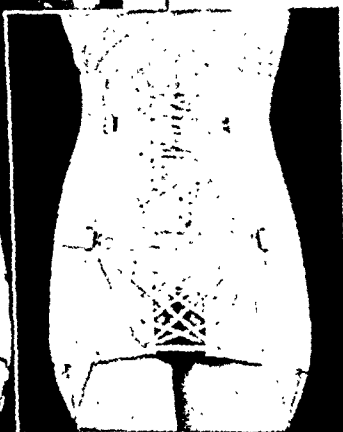
### Items

|   |     |
|---|-----|
| American Board of Obstetrics and Gynecology .....           | 923 |
| Central Association of Obstetricians and Gynecologists..... | 924 |
| American College of Surgeons.....                           | 924 |
| Books Received .....  | 924 |

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scientific curiosity continue to be born and to strive to answer the questions which will occur to their inquiring minds, it will continue to grow. A pinnacle will be added here, a turret there, until it approaches that state of complete knowledge from which we are still far away.

But little real advance occurred in medical science for centuries, and it was not until about four hundred years ago that substantial additions began to be made to the sum of available knowledge in the field of obstetrics and gynecology. For many years we looked to the Germans for scientific knowledge but a tremendous amount of valuable work was done by the French school in the sixteenth, seventeenth, and eighteenth centuries, and it is with some of these obstetric and gynecologic pioneers that I purpose now to deal.

The first man who stands out as a real contributor to the progress of obstetrics was Ambroise Paré. He was interesting not only as a contributor to general surgery, and to our own domain as well, but as a man. He was born, in all probability, as there is some little discussion about the date, in 1509, in the village of Bourg Hersent. His various biographers have debated as to the actual date of his birth but Le Paulmier, who has provided one of the best accounts of his life, has gone to some trouble to fix the date and believes that 1509 is the most probable one. His father was a chest maker, *coffretier* being the word used to describe his trade. No great amount of information is available as to his early years, but it is known that he had no knowledge of Latin and Greek. The lack of acquaintance with these languages was a great handicap to him for some of his contemporaries argued that, being ignorant of these, he could not study the old authorities and therefore could lay no claim to a knowledge of surgery. He himself made no secret of his lack of early education, nor did he permit it to keep him from accomplishing what he set out to do. From what may be found concerning his physical characteristics it seems that he was a man of middle stature, active, able to endure great exertion and fatigue, and seemingly spared from illness throughout his life. The only disability we find in his career is a fracture of both bones of the leg sustained by the kick of a horse which he was urging upon a ferry boat. The fracture was compounded as he stepped back to escape a possible second kick. This healed after a number of months of inactivity. He was bitten by a viper while watching the compounding of a remedy of which vipers formed a part but treated himself and recovered. An apparent attempt to poison him was made but he recognized the presence of the poison in time to cease swallowing the food in which it was before too much had been taken. He was somewhat quick of temper, a fault which he shares with many men of energy and nervous force. He seemed to like good living and was not at all averse to a glass of good wine, but there appears nowhere any record which would make it appear that he was a heavy drinker. He had a ready wit, which could

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## American Gynecological Society

Sixty-Seventh Annual Meeting, June 15 to 17, 1942

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### PRESIDENTIAL ADDRESS\*

#### THE INFLUENCE OF THE FRENCH SCHOOL IN THE SIXTEENTH, SEVENTEENTH, AND EIGHTEENTH CENTURIES UPON THE DEVELOPMENT OF GYNECOLOGY AND OBSTETRICS

W. C. DANFORTH, M.D., EVANSTON, ILL.

WE gynecologists and obstetricians today owe a great debt to our professional forefathers. The distinguished men who created this Society and who have maintained its reputation have set us an example which it is not easy to follow. They have done a great work in the development of gynecology and obstetrics in this country and Canada. Before their day, however, there were able workers who searched for facts and who strove to develop better methods of dealing with the ills of women. In the hurry of daily work and with the rapid development of knowledge we find it difficult to keep pace with what goes on today and the work of those who have gone before us is easily forgotten. In order that we may take a brief view of the work of a group who have contributed greatly to our science I ask you to come with me for a short time while we mount an imaginary hill from whence we may look backward over a part of the road our predecessors have traveled and to view, if we may, some of the work of the laborers who have built the foundations upon which rest the scientific structure within which we work. This scholastic edifice is not yet complete. So long as men of

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\*Delivered at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.

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Note: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

campaign, that he renounced the use of boiling oil and hot irons for the control of hemorrhage after amputations and from severe wounds. This was because the supply of hot oil failed and he had to have recourse to an emollient application made of egg yolks, oil of roses, and turpentine in its place. The improvement in results he instantly recognized and thereafter, against much opposition from his more statically minded confreres, refused to use them. In 1552, during the siege of Damvilliers, he amputated the leg of a gentleman in the suite of de Rohan, controlling bleeding by ligatures. The ligature had lain dormant since the time of Celsus, who described it in his seventh book. This controversy about boiling oil and the cautery produced for us a remarkable demonstration of his ability as a controversial writer for he was attacked



Fig. 1.—Ambroise Paré. Le Paulmier.

by Etienne Gourmelen who criticized severely his departure from the accepted methods. His reply, entitled an "Apology and Treatise," was not only an account of his travels and the surgical work which he found to do while accomplishing them, but was also a most biting and complete rebuttal, replete with sarcasm, calling attention to his own great practical experience compared with the largely academic knowledge of his opponent. Throughout this work he refers to his critic as "Mon petit maistre" which may be rather freely translated as "my little man." It is due to this attack upon Paré, and to his reply, that we know anything of Gourmelen. He was caught as a fly in liquid amber, and so preserved has come down to us. It was in this book that Paré

be trenechant at times. For example, when speaking of powdered mummy, which was a highly esteemed remedy in France in his time, he said that he believed mummies made in France would be as good as those which came from Egypt inasmuch as both were quite useless.

His independence of mind may also be illustrated by his attitude toward the use of the horn of the unicorn as a remedy. This was supposed to be an antidote to all poisons. He did not believe this and doubted even the existence of such an animal, for, he said, of all the men who had traveled in all parts of the known world there was not one who had even seen it. Moreover, the written descriptions varied widely from one another. His own experience showed him that it was without effect, and, in spite of the great value generally accorded it, he discarded it as a remedy.

He began his professional experience with three years' service in the Hôtel Dieu in Paris, a service of which he spoke with pride in after years.

He accumulated a large estate, a feat which not all of his followers have been able to equal, and, like many others who have achieved material success, had relatives whom he must help and some of whom lived in one or another of several houses which he owned in Paris. Much argument has appeared in the writings of those who have dealt with his career as to his religion. It seems to be without doubt that he was a very definitely religious and God-fearing man, but whether Catholic or Protestant, has been argued by a number of writers. The weight of evidence seems to be that he was a Catholic, but he does not seem to have made any public show of his belief. He was married in the church of his parish and his children were buried there.

That he was a man of wide knowledge and quite able to form opinions outside of his own domain seems to be evidenced by the answer of the Duke of Savoy to the French king who wished to send Paré across the lines between their two armies to attend a high officer who was wounded and a prisoner. The Duke refused, saying, "He knows other things than surgery," evidently fearing that entirely too accurate a description of the enemy military dispositions might be carried back to the French army.

His time was divided between service in the armies and practice in Paris, the disturbed state of the times in which he lived providing him with a large amount of military duty. He evidently went upon his first campaign at the age of twenty-seven because of a lack of money, a condition which still sometimes affects the young physician. He passed the examination for barber-surgeon in 1541, and in 1554, that for master surgeon. He apparently had to take the latter twice, but the reason for this is not known. He learned at least a modest amount of Latin before appearing for the Master's examination. His lack of classical learning did not depress him for, said he, Aesculapius wrote in his language and he, Paré, had the same privilege. It was in 1537, his first

military duty, he performed a great service to our specialty. His revival of version added tremendously to the resources of the accoucheur and was a great service to his patients, who before his time could only be delivered by traumatic destructive operations in the event that labor did not end spontaneously. His discussions of generation and of monsters were the first of which I know which directed attention to these subjects. In his discussion of generation he could, of course, give no accurate description of fertilization of the egg as the pioneer work in microscopy of Hooke in England, Malpighi in Italy and Leeuwenhoek in Holland was not to come for another century.

Here was a man of enormous energy and industry, unusual ability, who rose from humble beginnings through his own efforts to a commanding position in his profession and who contributed greatly not only to surgery in general but to obstetrics as well. We must regard him as one of the builders of the foundations of present-day gynecology and obstetrics.

He had some notable contemporaries, for Montaigne and Rabelais lived in France at the same time. He and Rabelais lived quite close together for a time, and it is strange that we find no mention of him in any of Paré's works. Indeed, he is said to have been a parishioner of Rabelais for a time. The French in which Paré wrote is quite the same as that of Rabelais. One whose knowledge of the language is sufficient to enable him to read easily the French of four hundred years ago will find great pleasure in reading him in the original.

He lived to old age and apparently his vigor of mind and his boldness remained with him, for in 1590, at the age of eighty-one, we find him addressing the powerful Archbishop of Lyon, during the siege of Paris, when there was much suffering among the people, and demanding that he use his influence for peace. That he attained a high position, not only professionally but also in society, we may know from the fact that the children of his second marriage had noblemen for god parents, the Duc de Nemours and the Marquis d'Elbeuf acting as such. He served three kings and Henri the second, the ablest of them, regarded him as a great friend. The successor of this king, Henri the third, a man of much less ability, he served with equal faithfulness evidently believing that duty was duty no matter who happened, by the accident of birth, to be the sovereign.

One of the most distinguished of the pupils of the famous master, Paré, was Jacques Guillemeau. He was born in 1520 and died in 1613. Other surgeons who had to do with his early training were Riolan and Courtin but of all his teachers, Paré left the deepest imprint. He had the advantage, lacking in the case of Paré, of an ample early education, and he was well versed in the ancient languages. It was he who translated the works of Paré from French into Latin in 1582. He had a love for belles-lettres and in every way seems to have been a scholarly man whose first interest was medicine. While he excelled Paré in learning

said "the operations of surgery are learned by the eye and by the touch." This polemic went on for some time for in 1593 Jean Des Hayes wrote a Latin thesis entitled "An Sistendo Sanguinem Ignis Vel Ligatura?" It was in his first campaign that we first find the expression so often quoted "I dressed him, God healed him." This expression is found in a number of places in his works.

In 1541 appeared his book, great in size as well as in matter. He gave a complete discussion of surgery as it was then known together with many illustrations. The excellence of the latter and the fullness of the index at the end of the book surprise the modern reader. In this work we find his discussion of the generation of man and a chapter on monsters. Some of these, as pictured in his book, might astonish the modern teratologist and seem to have been imagined, as Barry Anson puts it, by a combination of Genesis and genetics. Among the figures shown are some which resemble abnormalities familiar to us all but others bear no resemblance to fetal abnormalities as we know them.

In this work, in Book 25, Chapter XLVIII, appears an account of a woman who had a protrusion from the introitus, seemingly a prolapse. This was treated by an operation which appeared to be a vaginal hysterectomy. The woman died three months later, from a pleurisy as Paré says, and he was able to obtain an autopsy which disclosed the fact that no uterus was present. Apparently the operation must have done away with it. He pictures pessaries, both ball-shaped and in the form of rings. Remedies are given for vaginal and cervical conditions. An illustration appears of a speculum which is mechanically ingenious although less effective for the purpose for which such an instrument is used than those of today.

The cruelty of the hot oil and heated iron used for stopping hemorrhage repelled him, and we may assume that some of the obstetric procedures of his day must have been equally offensive. In 1549 we find his first reference to an obstetric subject. It is contained in a book published in that year and entitled "*Brief Anatomic Collection: with the method of setting bones: and of extracting infants, dead as well as alive, from the bodies of their mothers.*" This was printed in Paris at the sign of The Fat Hen. As he had to leave soon after this was submitted for publication, the errors in the text were corrected with the pen. In this work we find the first reference to podalic version. In 1573 he published a book entitled "*Dix Livres de Chirurgie avec le Magasin des Instrumens necessaires a icelle*" (10 books of surgery with the necessary instruments). Here we find pictured a few of the hooks and curved knives employed to terminate impossible labors. Forceps were not to appear for another century, and we may well imagine that these implements and the procedures carried out with them may have impelled him to seek a better way of terminating these cases.

While only a small part of his time was devoted to obstetrics, and this necessarily during that portion of his life which was not filled with



temporized in the hope that bleeding would cease." This may awaken memories in the minds of many of us who have met this sort of thing in our professional careers.



Fig. 3.—The pregnancy and delivery of women. Guillemeau, 1620. (Courtesy of Surgeon General's Library.)

His life resembles that of Paré in that his professional experience began in the Hôtel Dieu where he served as a young man at the outset of his career and in which he, for a time, did military duty. While the inventive genius and initiative of his master were absent, he must still

outside the field of surgery, and while he was a faithful and skillful follower of the teachings of his master, we find no evidence in his career of the bold, restless, scientific pioneer, seeking new truths and eager to try new methods. He took what he had been taught and used it excellently but added nothing to it, except a work on the diseases of the eye. This, however, was not too highly considered by his contemporaries and by later authorities is not regarded as an outstanding piece of work. In obstetrics, he took the operation of version, which he had seen carried out by Paré, and used it to good purpose. It is said that he saved the daughter of Paré by version when she was bleeding seriously.



FIG. 2.—Jacques Guillemeau.

In 1609 he published a book entitled *L'Heureux Accouchement des Femmes* and in 1621 another entitled *De la Grossesse et Accouchement des Femmes, du gouvernement d'icelles, et moyens de subvenir aux accidens qui leur arrivent* (*The Pregnancy and Delivery of Women, Their Management, and the Means of Dealing with Complications*). This last was his best work.

Guillemeau favored version but condemned cesarean section, with which opinion we should probably agree, if we were to work under exactly the conditions of his day. He states that "the worst things which can happen to a woman in labor are hemorrhage and convulsions. If either one occurs, immediate delivery is needed." In speaking of the loss of patients from obstetric accidents he says, "We have seen, to our great regret, death occur because of the stubbornness of relatives and friends, or even by the fear of doctors and surgeons, who

of these had been published before but by the time this edition appeared the number had grown to 700. He exhibited a commendable broad-mindedness in these reports for he included a number of cases the outcome of which had not been favorable. These he characterized as things to be avoided, those which were successful being things to imitate.

He condemned cesarean section and made extensive use of version. He illustrates in his book a number of knives and hooks which he used when he was compelled to make use of a destructive operation. Among

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Tradens veram optimamque methodum adjuvandi Mulieres  
in partu naturali, & medendi culibet partui contra naturam,  
morbisque infantium recens-natorum; cum accurata descri-  
ptione omnium mulieris partium generationi inservientium;  
adjunctis multis figuris æri egregie inculptis.

*Opus Chirurgis utilissimum, Obstetricibusque omnibus ad obstetricandi  
artem perfecte discendam rualde necessarium.*



PARISIIS,

Apud AUCTOREM, in medio vix dictæ des Petis-Champs, sub signo boni Medici.

M. D. C. L X X X I.

*Cum Privilegio Regis, & Approbatione Domini Archiatrorum Comitiss.*

Fig. 5.—First Latin edition of Mauriceau, 1681. (Author's collection.)

his case reports we find, in observation 26, the account of his meeting with Chamberlen and of the latter's vain attempt to deliver a rachitic dwarf who was under Mauriceau's observation. He concludes the report with the observation that the English obstetrician had gone back to London from Paris where there were more skillful accoucheurs than he. This unfortunate patient died of a ruptured uterus the next day and autopsy showed numerous wounds of the uterine wall made by the forceps, which as Mauriceau explains, had to be introduced without the guiding hand as the pelvis was so small. The experience caused him to devise an instrument he called the "tire-tête" by means of which he believed that such cases could in future be managed. The modern

be accorded a place among the real builders of our specialty, for he continued the work of Paré in adding version to the resources of the accoucheur, both by his work as a widely known practitioner and as the author of two authoritative books.

In the seventeenth century appeared a leader and teacher of the art of obstetrics, Mauriceau. He obtained a large early experience in the Hôtel Dieu in Paris. Details concerning his life are difficult to obtain but he seems to have carried on a very large practice in Paris and to have served extensively in the capacity of what we should today term



Fig. 4.—Mauriceau. (Author's collection.)

an obstetric consultant. His basic principle was that an exact knowledge of the anatomy of the reproductive tract and its function must underlie any obstetric teaching. With this statement none of us will disagree. In his own published work, however, we may regret that he did not make use of anatomic investigations of his own rather than follow the old dissectors. Fresh material of his own providing would have been a great addition to his valuable work. In 1668 appeared his book, containing the description of the reproductive anatomy, obstetric technique, management of the puerperium and of the newborn. This book went through a number of editions, the first being in Latin, in which the edition of 1681 was also printed. The edition of 1694 appeared in French and to this was added a large number of case reports. Some

None the less, he was a great man and perhaps many of us have seen men who have had the same fault without as much justification as had Mauriceau.

Professional differences of opinion in the seventeenth century brought forth a greater freedom of expression than we today feel is proper. Mauriceau spoke his mind in plain terms in a number of instances. The following, concerning the work of one of his contemporaries, Viardel, may serve as an example: "The notable error of a modern author, whose book deserves rather to be sent to the butter sellers and grocers of the public market to be used as wrapping for their merchandise than to be distributed to the public to be the cause of dangerous consequences because of his bad precepts, and because of the crass ignorance of the author, whose method is pernicious."

The second half of the seventeenth century was distinguished by the appearance of a number of able workers. Mauriceau was the greatest but other lesser suns shone in the obstetric sky. Louise Bourgeois followed the work of Paré and Guillemeau and insisted on the advantages of version and rapid intervention in cases of hemorrhage. She also insisted on the possibility of delivery in face positions. Pineau studied the anatomy of the pelvis and drew attention to the abnormalities caused by rachitis.

The most notable of those who appeared at this time was Paul Portal. The date of his birth is not exactly known but was probably 1630. There is a hiatus in the public records of Montpellier, where he was born, of about ten years. During this time Portal was born. He entered the Hôtel Dieu in 1650, admission to which was not permitted under twenty years of age. One of the best sources of information concerning him is a thesis submitted for the doctorate in medicine in Paris in 1900 by an aspirant named Maruitte. As the thesis was passed upon by a committee presided over by Pinard we may assume that it is essentially correct. Of his early life we know little but that he became what we should term today a resident in the Hôtel Dieu in 1657, leaving it in 1663. The teacher of whom he speaks the most was René Moreau, and to him he dedicated his book. Copies of this are rare today and Maruitte speaks of the difficulty he experienced in obtaining a copy to use in preparing his thesis. He finally used one which had belonged to Tarnier. I have not been able to find a copy of the original French edition but did find one of the English edition printed in London in 1763. The French title was *Pratique des Accouchements* while the English edition bore the title *The Compleat Practice of Men and Women Mid-wives, or the True Manner of Assisting a Woman in Child-bearing*. The book itself is quite short and entirely clinical in character. It is accompanied by a number of observations in the manner of Mauriceau's book, although the number of cases cited is less. He intended it to be a record of his own experience and says that it is to be "not only what authors have written but what I have seen." This manifests a healthy

operator, looking at the drawings of the instrument, may perhaps have some doubt as to its efficiency. One may wonder what the effect upon obstetric progress would have been if the case given to Chamberlen had been a more favorable one and had succeeded. If Mauriceau had accepted the instrument, with his commanding position and his great energy, it would have been made known to the medical world far sooner than it was. We cannot commend Chamberlen for trying to sell the forceps, but this operative failure withheld the help it could give to many women for years.

Chamberlen was sufficiently impressed by Mauriceau and his work that he translated his book into English. The English version was published in London in 1716.

He was acquainted with placenta previa and reports a number of cases. He did not recognize the exact state of affairs, however, for he believed that the placenta had become loosened from its normal seat and had preceded the child into the lower part of the uterus.

Although he was an acute observer and a skillful operator, we are told that even Jove may nod, and so we find him denying the work of de Graaf and refusing to believe the existence of the egg in the ovary. He carried his skepticism so far as to deny tubal pregnancy although he saw at least one which he described and illustrated in Book I, Chapter 5. He believed that the swelling in the tube was a hernia of the uterus. I cannot take the time to go into all his explanations of the findings in this case but he goes into the matter in detail and indicates how he believed the fetus escaped through a tear in the side of the uterus.

His greatest service was in definitely establishing the technique of breech extraction, particularly of the delivery of the aftercoming head. His description of this operation in Chapter 13 of Book II should be read by every obstetrician as it is one of the important contributions to our art. His name alone should be attached to this operation without the addition of those of others who merely "re-discovered" what had already long been known.

As many great men, he also had a few foibles, which we may easily forgive. He seems to have had a rather active appreciation of his own worth, which, the circumstances being what they were, is far less of a fault than if he had been a mediocrity.

In the frontispiece of the edition of 1681, we find, under a small portrait of himself, the words, "*Me Sol, non Umbra, regit.*" His finger points toward the sun. The implication seems to be that he thought some of his contemporaries were less happy than he in their choice of a source of inspiration. In his case reports, too, we occasionally find an expression of the same feeling when he remarks that he did this or that to the great amazement of the midwives and surgeons present.

in the corpus uteri and therefore seems to have been the first to appreciate the true nature of placenta previa. Mauriceau had taught that face presentation, when left to itself, will often terminate happily but the lesson had not been completely learned. Portal, who re-emphasized this important fact, did much to fix it in obstetric teaching.

Among his case reports is one of a hydatidiform mole of which he gives an illustration. His description is accurate. He speaks of the vesicles as resembling white currants, or the spawn of frogs. He took the specimen home with him for study and invited M. Auzon, of the Faculty, to see it with him. He does not give the date of this observation, but, as in many of his case reports, he gives the name of the street in which the patient lived. The patient recovered.

He also pointed out the possibility of accomplishing a breech delivery by means of one foot only. The extraction already described by Mauriceau is spoken of, the technique given, and he used it himself.

His book, which was overshadowed by that of Mauriceau, which was still recent, and which went through a number of editions, did not receive the attention it merited. Nonetheless, he must be reckoned among the builders of our branch of medicine.

Among the teachers of the eighteenth century two figures stand out, those of Levret and Baudeloque. André Levret was born in 1703 and died in 1780. He devoted himself with enthusiasm to the improvement of obstetric technique. In 1739 he received a legacy from a patient, a man, by the way, whom he had cared for over a considerable period of time and who showed his appreciation by leaving him a sum sufficient to free him from the need of earning his entire living. He was on terms of great friendliness with Louis, chief surgeon of the Salpêtrière and later permanent secretary of the Royal Academy of Surgery, with whom he made a number of reports. After the death of Jard, accoucheur of the court, Levret followed him in this office. Numerous students came to him from near and far, through whom, together with his writings, his name and teachings became widely known in his own country and elsewhere. He was particularly interested in improving the technique of operative obstetrics and in 1747 devised a forceps by the use of which he hoped to obviate the need of always locking the instrument at the same point. This he accomplished by the use of three holes in the shank, through any one of which locking could be accomplished, the blades being joined at the desired point by means of a peg held in place by a small rod. The movable point of locking, in principle, is not unlike that of the forceps of Kielland, which appeared about 165 years later. The instrument still left something to be desired and in 1748 he added the pelvic curve which since his day has never ceased to be a part of the obstetric forceps. The drawings of these instruments are accurate and would serve as excellent specimens of mechanical drawing today. This modification of the forceps constitutes his great addition

spirit of observation which contrasts with the writings of many authors who are content to take what has been written by others and to repeat it as their own and thereby prolong error.

We find in the records of his work evidence that he was an excellent clinician. His judgment as to the management of some of the complications of labor would be agreed to by most of our modern teachers. His advice against attempts to hasten labor may well be listened to today and his warning against interference without adequate cause resembles some of those which have been uttered in the past few years. His attitude toward medical literature is shown by his statement that "books would be of more value if they reported what has been seen and done, these things being told with sincerity and good faith."



Fig. 6.—Paul Portal.

Portal differed from Mauriceau in that he was pacific and not given to forceful expression of differences of opinion. He commonly refers to his contemporaries as skillful surgeons and able physicians, and we find no severe criticisms of their work. He did not enjoy a practice made up largely of the wealthy or socially prominent; most of his patients, as Maruitte tells us, being the wives of tailors, shoemakers, grocers, and so on. However, clinical experience is as well, if not better, gathered in the lower ranks of society, and we know that the "fashionable physician" in many large communities today is often not a contributor to the science of medicine.

He genuinely contributed to our specialty. He recognized, as Mauriceau and Paré had not, that the placenta may attach elsewhere than



*proposé ou mis en ouvrage pour les terminer, et de nouveaux moyens pour y parvenir plus aisément* (observations upon the causes and complications of various difficult labors, with remarks upon that which has been proposed or used to terminate them, and concerning new means for accomplishing this more easily) appeared in 1747. A number of editions followed, a third revised one in 1762 and a fourth in 1770. Another notable work was his *L'Art des accouchemens démontré par des principes de physique et de mécanique pour servir d'introduction et de base à des leçons particulières* (obstetric art demonstrated by physical and mechanical principles to serve as introduction and as base for private lessons), which was published in 1761.

An anecdote survives according to which, when he came to care for the wife of the brother of the king during labor, her husband, known as "Monsieur" during the days of the Bourbon kings, condescendingly said to him, "this case will make your reputation." Levret at once replied, "If my reputation were not already made, I should not be here."

Among his publications is one on polyps, which appeared in 1749 and which does not confine itself to polyps of the uterus but includes those of the throat and nose.

He was a great teacher who was not only a skillful operator but who also considered the mechanical problems which delivery sometimes presents and who went about solving them in a logical manner. His great addition to the art of the forceps will probably remain permanently in the literature of obstetrics.

The second great figure of the eighteenth century was Baudelocque. He was born in the town of Heilly, in Picardy, in the Department of the Somme, in 1746. His medical studies were carried on in Paris where he worked especially in anatomy, surgery, and obstetrics. His teacher in obstetrics was Solayres with whom he became very friendly. On one occasion Solayres, who became ill, had Baudelocque take over an unfinished course and complete the instruction. After the death of Solayres, Baudelocque continued teaching. He became a member of the "College de Chirurgie" in 1776, his thesis being entitled "*An in Partu propter Angustiam Pelvis impossibili symphysis ossium Pubis secanda?*" I have not been able to find a copy of this, but it is said to have placed a proper evaluation of this procedure before his countrymen. When the Faculté de Medecine and the College de Chirurgie disappeared the École de Santé was founded and Baudelocque and Leroy became teachers of obstetrics. In 1798 he became Chief Surgeon and Accoucheur of the newly built Maternité and began the teaching of midwives. He had the confidence of the public and toward the end of his life Napoleon named him First Accoucheur of the Empress. He did not wholly escape vilification, as many eminent men have not, and was attacked in court after the death of a patient following delivery, and this through the action of a confrere named Sacombe. Baudelocque was acquitted while his colleague was fined 3000 francs. French justice in the

to the field of operative obstetrics and one which remains with us still and which will probably never be displaced.

The mechanical ingenuity of the man may be demonstrated by the drawings of his three-bladed instrument designed for the extraction of the head left in the uterus after attempts at breech delivery, an accident seemingly more common then than in good clinics today. His sheathed

# OBSERVATIONS

SUR

LES CAUSES ET LES ACCIDENS

DE PLUSIEURS

ACCOUCHEMENS

LABORIEUX,

AVEC DES REMARQUES

Sur ce qui a été proposé ou mis en usage pour les terminer;  
& de nouveaux moyens pour y parvenir plus aisément.

Par M. A. LEVRET, du Collège & de l'Académie  
Royale de Chirurgie, Accoucheur de Madame la  
Dauphine, &c.

Troisième Edition, revue & corrigée.

*Alexandre Viennois*

A PARIS,

Chez P. ALEX. LE PRIEUR, Imprimeur du Collège  
& de l'Académie Royale de Chirurgie, rue  
Saint Jacques à l'Olivier.

M. DCC. LXII.

*Avec Approbation & Privilège du Roi.*

Fig. 7.—The treatment of difficult labor, Levret, 1762. (Author's collection.)

hook (*crochet à gaine*), was another device of a mechanical mind. That the two latter instruments have not survived is no criticism of the outstanding value of his addition to the forceps. This improved instrument decreased the number of destructive operations. Time does not permit the discussion of all of his contributions to the art of operative obstetrics, but Siebold's statement that he must be regarded as the founder of a rational teaching of operative obstetrics seems just.

His book, entitled *Observations sur les causes et les Accidens de plusieurs Accouchemens laborieux avec des remarques sur ce qui a*

Baudelocque had about 150 of these students a year. They were taught far more completely than is the case with their sisters of today, for they were taught to do the operation of version and that of forceps. This was accompanied by instruction in the fundamentals of obstetrics and embraced even vaccination, bleeding, and something of pharmaceutical botany. The public institutions were so taken up with the teaching of midwives that physicians wishing to increase their knowledge of obstetrics had to go to smaller private institutions. The Maternité, in Baudelocque's day, had about 2000 births a year, which were used solely for the teaching of the midwives. Since these women, after their course of instruction, were scattered over all of France, Baudelocque's principles obtained a wide recognition.

When many of us were students there were published small books on many subjects which consisted of question and answers. These were known as quiz compends. Whoever published the first one may have thought he had an original idea but in 1775 Baudelocque published a book for midwives constructed on exactly this principle. This appeared in various editions and in 1787 the Government had 6000 of them printed. In 1806 another edition was needed. Two more followed and translations were made into German and Italian.

Baudelocque carried the obstetrics of the eighteenth century over into the nineteenth, and, as Cutter puts it, integrated the best French teaching with the rapidly developing English school led by Smellie. His teaching was upon sound principles and his training of midwives, whatever we may think of them as a class today, probably was the means of bringing to a great number of French women better care than they would otherwise have had. While other able men worked in the eighteenth century Levret and Baudelocque seem to stand apart from the rest and to have accomplished more than any other two.

Paré seems to have been the one to first attack the problem of delivery in difficult labor without in every case sacrificing the infant. Before his day, medicine had slumbered for centuries. While his own work consisted in the re-establishing of the operation of version, he succeeded in bringing the question of the management of difficult labor before the medical world and all the progress which has brought us to where we are today began with his work. Baudelocque regarded Mauriceau as the first real accoucheur and after him came a group of brilliant workers whose work remains in the structure of modern gynecology and obstetrics. In the nature of things but little of the work of these men was gynecologic, for aseptic surgery was still far away. Their work was fundamental; they laid some of the great foundation stones upon which later workers might build. The French nation today has fallen upon evil times and no one knows when, if ever, it may regain something of its former intellectual leadership. But in the days in which lived the men of whom I have spoken the French were a great people and their contributions to science were of great value. We

eighteenth century seems to have possessed an acuter vision than some which we have known since that time. The memory of this affair embittered him until the end of his life. He died in 1810.

He gave much attention to the mechanism of labor and to deformities of the pelvis and devised a "Compas d'épaisseur" which was simply the beginning of the pelvimeter. While he made use of version extensively, he by no means scorned the forceps and devised one of his own which was somewhat longer than that of Levret. He was concerned in establishing definite conditions under which the instrument should be used. The problem of too frequent interference seems to have been present then as now.

**PRINCIPES**  
**SUR L'ART**  
**DES ACCOUCHEMENS,**  
*PAR DEMANDES ET REPONSES,*  
**EN FAVEUR DES SAGES-FEMMES**

DE LA CAMPAGNE:

*NOUVELLE EDITION, revue, corrigée,  
augmentée & enrichie d'un grand nombre de  
Planches en taille douce, propres à en faciliter  
l'étude;*

PUBLIÉE PAR ORDRE DU GOUVERNEMENT:

*PAR M<sup>r</sup> J. L. BAUDELOQUE, Membre du  
Collège, Conseiller du Comité perpétuel de l'Académie  
royale de Chirurgie de Paris...*



A PARIS, -  
*Chez M<sup>e</sup> ÉQUIGNON l'aîné, Libraire, rue des  
Cordeliers, près des Écoles de Chirurgie,*

M. DCC. LXXXVII.  
*Avec Approbation & Privilège.*

Fig. 8.—Text Book for Midwives by Baudelocque. (Author's collection.)

He did a great work in the teaching of midwives. Most of these women were sent by their departments, being chosen by the prefects, for instruction so that they might return home and serve their own communities and hospitals. These schools of midwifery were useful institutions in the eighteenth century and the famous women who taught at that time worked in them as head midwives. Madame La Chapelle and Madame Boivin are the chief examples. Unfortunately, the time available will not permit my speaking of them at length.

## STUDIES ON HEAD MOLDING DURING LABOR\*

HOWARD C. MOLOY, M.D., M.S.C., NEW YORK, N. Y.

*(From the Department of Obstetrics and Gynecology, Columbia University and the Sloane Hospital for Women)*

IT IS a well-known fact that during labor the size of the area enclosed by the circumference of the fetal head slowly decreases through flexion and molding. For this reason investigators, using roentgen methods of mensuration, have difficulty in finding an accurate method of determining head size and active research continues. Other workers doubt if this problem can be solved and believe that obstetrical prognosis, for borderline cases at least, will continue to depend upon a trial of labor to disclose the true significance of the supposed degree of existing disproportion between the head and the pelvis. We have been interested in this problem of cephalometry for some time and believe that ultimately methods will be devised which will bring about greater accuracy in prognosis. In the meantime, a chance observation has directed our interest toward the question of head molding. This observation suggested the possibility that certain changes might occur in the base of the skull, a region hitherto considered too rigid to be modified significantly by the forces of labor. The present investigation has developed from this original observation.

### METHODS OF STUDY

At birth, both in the molded head and the head delivered by cesarean section, the coronal and lambdoidal suture lines are either closed or show very slight separation (Fig. 1). A separation at these suture lines begins shortly after birth and increases rapidly in the postnatal period (Fig. 2). This postnatal separation causes an increase in certain diameters (occipitofrontal) in addition to the increase or decrease produced in other cephalic diameters by the disappearance of the physical effects of molding. For this reason, molding cannot be studied by comparing the shape of the head at birth to the shape assumed later in the postnatal period.

Another factor which must be considered in the study of molding refers to the bending caused by the squeeze effect of labor. The magnitude of the changes caused by the squeeze effect of labor upon the head is probably greater than is realized. For instance, we have found that the biparietal diameter immediately increases by at least one-half

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today are finishing the structure which they, and their co-workers in other lands, began. Most of the great principles have been established but much remains to be done in the perfection of technique and the furthering of knowledge along physiologic, biochemical, and endocrinologic lines. In the progress which has been made in the last half century, the Fellows of this Society have borne a notable part. It is certain that the contributions of the Fellows of the future will solve some of the remaining problems. At a time in which the resources of the Nation and the lives and careers of our young men are being devoted to the struggle against the forces of destruction, we are permitted, because of the age of most of us, to continue the constructive work of medical science. May we so conduct ourselves that not only we may follow well the example set us by some of those who have worked in centuries gone before but that we may maintain our Society in that high place in which our eminent predecessors have left it.

When not otherwise indicated, illustrations are by the courtesy of the Church Library of Northwestern University Medical School.

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centimeter as soon as the head is born. The spring effect of the constriction of the head by the maternal passages no doubt disappears very rapidly after birth, so that it is important to obtain the roentgenologic examination as soon as the condition of the newborn child permits. Examination of the newborn child immediately after birth reveals a mobility of the bones of the vault and even of those constituting the base which cannot be demonstrated to advantage within one hour.

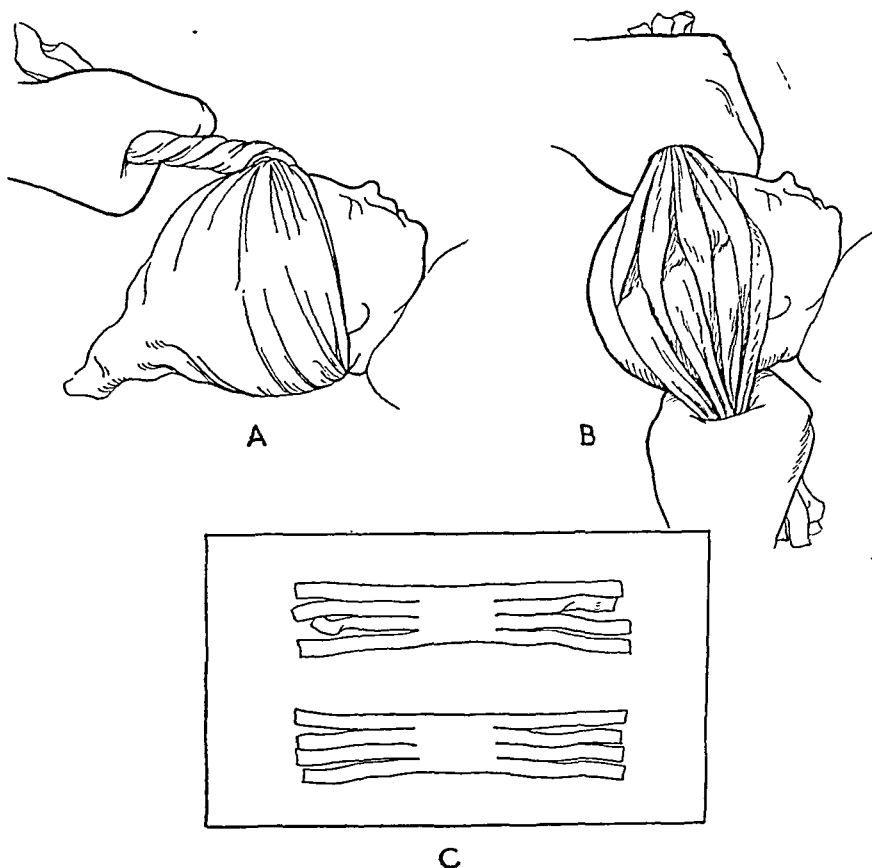


Fig. 3.—Methods of compression. *A*, The towel compression binder used to simulate the squeeze effect of labor upon the living infant. The constriction force was not measured except by a crude index of six and one-half turns of the towel. *B*, Method of compression binder used upon stillborn heads. A strong constriction force, not measured, was used. *C*, Diagram of the interlacing type of binder used in method *B*.

Although this fact was soon realized, it was found to be impossible in most instances to obtain the roentgenologic examination within the first hour of life because it was necessary to allow the infant to recover from the effects of delivery and time was consumed in transit to the roentgenological department for the examination.

In an effort to simulate the squeeze or bending effect of the forces of labor, a compression binder was used as illustrated in Fig. 3. This method of towel compression exerts its maximum effect between the brow and the suboccipital region. The amount of compression used was not measured except in a gross manner as expressed by six and one-half turns of a towel.

We have, therefore, used the following two methods for determining the effect of labor on the head.

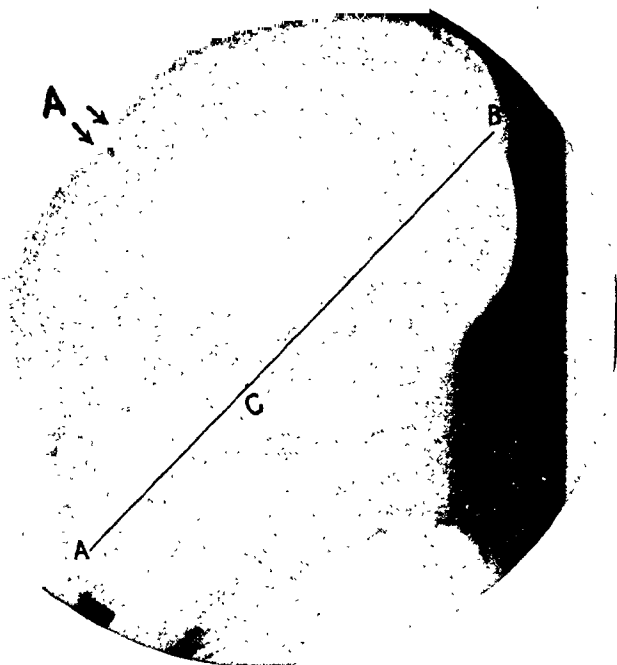


Fig. 1.—Lateral view of a markedly molded head shows closure of the coronal "A" and lambdoidal suture lines. Forward displacement of the occipital plate is apparent with overlapping at the lambdoidal suture, because, in the postnatal period, there is no compression of the parietal bones to restrict the degree of this movement. Note asymmetrical separation of lateral suture line (retouched).

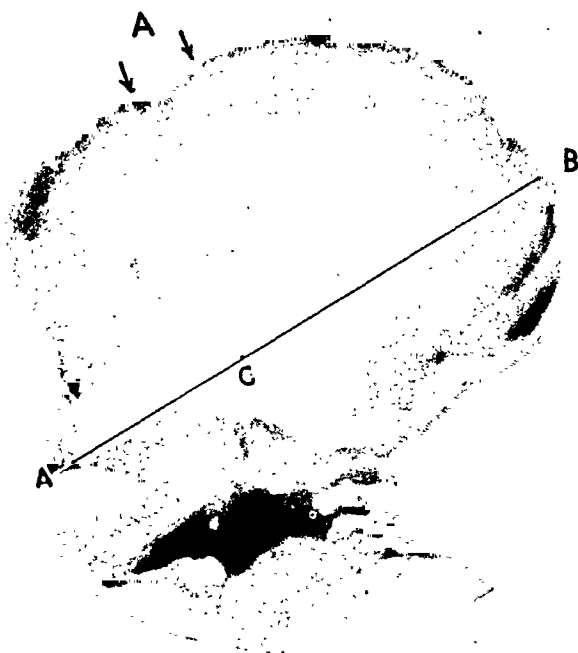


Fig. 2.—Lateral view of the example shown in Fig. 1 eleven days after delivery reveals separation of the coronal "A" and lambdoidal suture lines. Compare the level of the tip of the occipital bone to the maxillary-spheno-occipital line, *ACB*, in the two views.



It is true that this landmark may be readily identified in most lateral roentgenograms, but the dorsum sellae is a more definite and easily recognizable landmark. Accordingly, a "sphenovertical diameter," *AB*, is described, extending from the midpoint of the upper border of the parietal bone to the dorsum sellae. Another diameter which is discussed in this presentation extends from the midpoint of the upper border of the parietal bone to a point in space between the tips of the superimposed petrous portions of the temporal bone. This distance is termed the "midpetrovertical diameter," *BD*. It will be pointed out later that the angle diverging from the suture line between the sphenoid bone and the basiocciput is modified by molding. This angle is designated as the "sphenopetrous angle," angle *F*, Fig. 4.

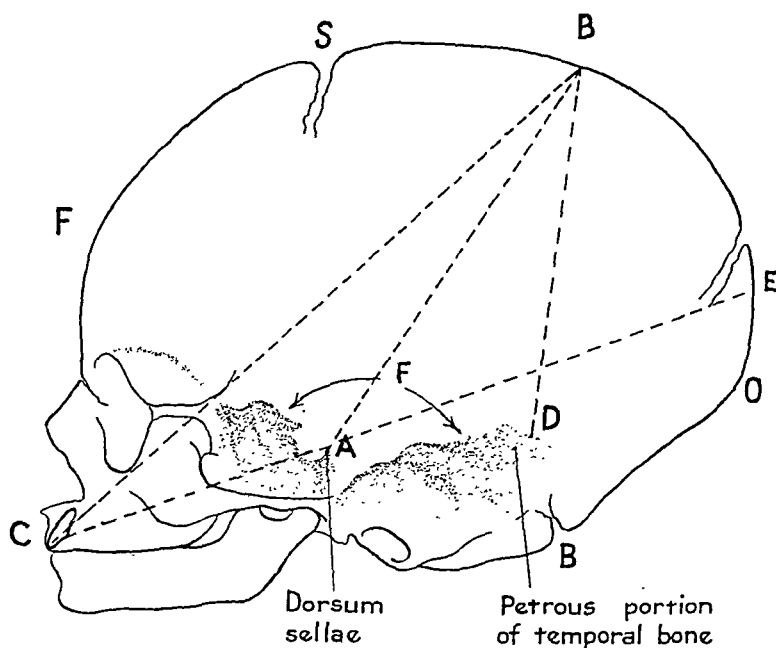


Fig. 4.—Diameters of the fetal cranium modified by molding and applicable for the study of lateral roentgenograms. *CB*, Maxillary-vertical diameter. *CAE*, Maxillary-spheno-occipital diameter. In the molded heads the tip of the occipital bone is usually at least from one-half to one centimeter above this line. Immediately after birth the tip begins to recede toward the level of this line, and in adults, it is depressed below this line. *AB*, Sphenovertical diameter. *BD*, Midpetrovertical diameter. *FO*, Occipitofrontal diameter, *SB*, Suboccipitobregmatic. *F*, Sphenopetrous angle.

A study of the base of the skull (Fig. 6) draws attention to two suture lines which may allow bending within the skull base; the suture line between the sphenoid and petrous portion of the temporal bone and basioccipital bone "A," and the suture lines between the basioccipital bone and the occipital condyles "B."

As an aid in explaining an interesting mechanism of locking which can be demonstrated at the coronal and lambdoidal suture lines, two transverse diameters are described which are relatively unimportant for any other purpose. These two diameters are termed the "anterior-inferior-biparietal" and the "posterior-inferior-biparietal" diameters (Fig. 5). The former extends between the anterior-inferior border of the parietal bones at each anterior lateral fontanel. The latter extends between the posterior-inferior borders of the parietal bone at the

1. The comparison of films obtained immediately after birth by cesarean section with those obtained with heads delivered through the maternal passage.
2. The comparison of films obtained from molded heads before and after the use of a compression binder.

Lateral roentgenograms and, in a few instances, anteroposterior exposures were obtained as soon after delivery as possible. During the earlier part of the investigation a target-film distance of six feet was used in 33 case studies. Later a shorter target-film distance was employed in approximately seventeen cases. Likewise a shorter target-film distance was used in approximately fourteen cases which were subject to compression to simulate the squeeze effect of labor.

Although 64 complete roentgenologic studies were made on newborn infants, several factors existed which limited the number of cases suitable for study purposes. In most instances, the physical evidence of molding in the vault and skull base was slight because no disproportion existed between the head and pelvis. Good examples of molding occur in premature infants due to soft part compression and in average-sized infants due to the presence of definite degrees of disproportion. In the latter circumstance the disproportion is overcome by effectual labor in conjunction with adequate flexion and molding. At the present time, cesarean section is employed not infrequently for moderate degrees of disproportion and the head is not given a chance to mold. For these reasons the number of extreme examples of molding adequate for study purposes in a series of sixty-four cases is not great. In not a few instances a case study was excluded because it is difficult to maintain a newborn child in a fixed position long enough to obtain a perfect lateral view with satisfactory superimposition of the orbital ridges, the petrous portion of the temporal bones, and the coronal and lambdoidal sutures. This difficulty is increased with any attempt to use compression. A compression binder was used in 14 instances, and although the observations reported in this presentation could be demonstrated in all these cases, satisfactory lateral views from examples of extreme molding were obtained in only two instances in living infants, one of which is illustrated in Figs. 15 and 16.

#### A. CEPHALIC DIAMETERS

It is necessary here to define certain head diameters which are not illustrated in most obstetrical texts. The well-known occipitomenal diameter is not satisfactory for the purpose of this study inasmuch as it is impossible to control the position of the lower jaw during the roentgenologic examination. We have chosen a diameter which is somewhat comparable to the occipitomenal diameter and which extends between the upper incisor tooth and the midpoint of the parietal bone along the median sagittal suture (Fig. 4). This distance is termed the "maxillary-vertical diameter," *CB*. A line drawn from the tip of the upper incisor tooth through the tip of the dorsum sellae and extended to the circumference of the skull posteriorly may be termed the "maxillary-spheno-occipital diameter," *CAE*. It is also desirable to use a single diameter to express the distance between the vault and the base of the skull. Scammon and Calkins have described the vertical auriculo-vertex distance extending from the midpoint of the parietal bone along its upper free border to the plane of the external auditory meatus.

posterior lateral fontanel. When slight but uniform pressure is applied over each parietal eminence of a living newborn infant, all transverse parietal diameters are reduced in size and the median sagittal suture closes and may overlap. Under these circumstances, the anterior-inferior-biparietal diameter is shorter than the bifrontal diameter and the posterior-inferior-biparietal diameter is shorter than the width of the base of the occipital plate (bi-occipital diameter). This fact can be demonstrated easily in the newborn infant when pressure is applied at the parietal eminences. The lower third of the occipital bone overrides the adjacent border of the parietal bones and, in front, the frontal bones override the adjacent lower aspects of the anterior border of the parietal bones just above the anterior lateral fontanel.

#### B. METHOD OF FILM COMPARISON

Two fixed points, the tip of the dorsum sellae and the most prominent upper incisor tooth, were chosen within the head in order that landmarks around the circumference of the head as shown in a lateral roentgenogram may be compared to each other under identical conditions. For tracings and for comparison of any two individual lateral roentgenograms, the sharp tips of the dorsum sellae on the two films are first superimposed and the upper incisor tooth on one film is shifted to meet the line joining these two points on the other.

#### OBSERVATIONS

*A. Comparison of Molded and Unmolded Heads.*—It is possible to identify with accuracy on a lateral roentgenogram the following cardinal landmarks which are commonly displaced in molding; i.e., the points of origin of the occipito-frontal diameter, the posterior-superior angle of the frontal bones at the anterior fontanel, the midpoint of the free edge of the parietal bone along the median sagittal suture, the tip of the occipital bone, the posterior-inferior edge of the occipital condyles at the base of the skull, and the superimposed tips of the petrous portions of the temporal bone. The direction and degree of displacement of these landmarks may be appreciated by comparing their relationship in a series of heads demonstrating marked molding with a small series of unmolded heads delivered by cesarean section (Fig. 7). The small number of cesarean section cases used in this diagram is explained by the fact that these cases were selected from the series as a whole upon the requirements of the following factors; a six foot target-film distance, average size child, vertex presentation, and the employment of either the elective type of operation or operation after a very short trial of labor.

A study of this composite diagram draws attention to the following points which indicate the trend in molding and warrant more detailed consideration.

1. The most marked change caused by molding is indicated by the variations in the position of the mid point of the upper border of the parietal bone at the highest point of the vault (*C*, Fig. 7). This change indicates an increase in the maxillary-vertical and sphenovertebral diameters.

2. The variations in the position of the midpoint of the vault of the skull (forward and backward range) would seem to indicate that the

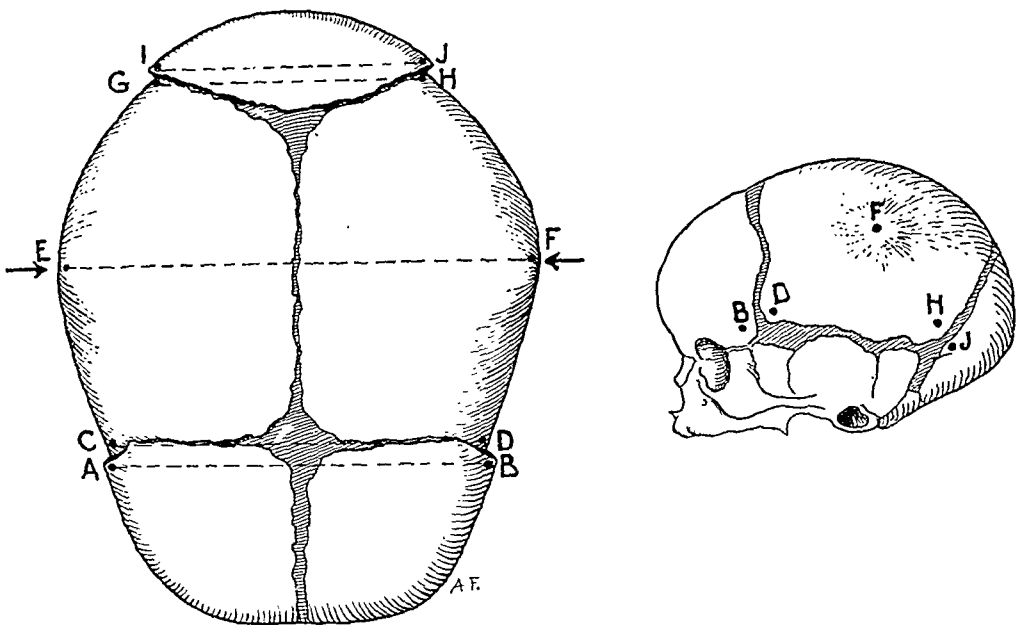


Fig. 5.—Diameters of the fetal cranium modified by molding. Vertical view. *AB*, Bifrontal diameter. *CD*, Anterior-inferior-biparietal diameter. *EF*, Superior-biparietal diameter. *GH*, Posterior-inferior-biparietal diameter. *IJ*, Bi-occipital diameter. Lateral view (insert) shows relative location of these transverse diameters.

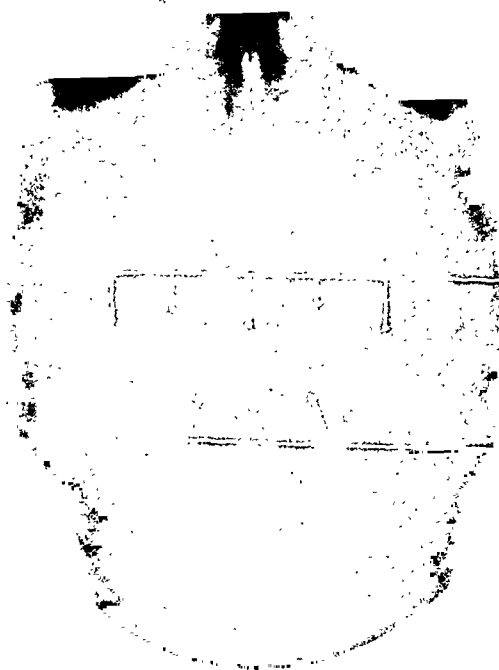


Fig. 6.—Important suture lines within base of skull. *A*, The suture line between the sphenoid and the petrous portion of the temporal bone and the basioccipital bone. *B*, The suture line between the basioccipital bone and the occipital condyles.

our present concept of the mechanism of head molding. This concept has been described accurately by Holland as follows:

"The head consists of a nonrigid shell composed of loosely joined plates of pliable bones joined to a rigid base. The greatest bending of individual bones occurs in the parietal and frontals; the occipital bone

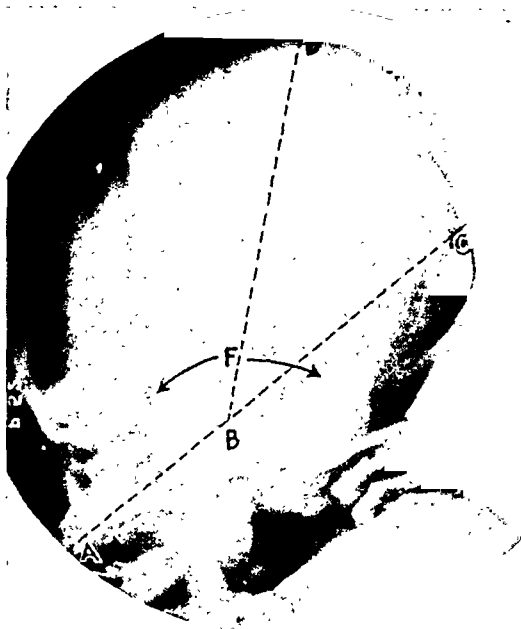


Fig. 8.—Lateral view of a well-molded fetal head. Note the acute sphenopetrous angle ( $F$ ), and the long sphenoververtical diameter ( $BD$ ), and the long maxillary-vertical diameter ( $AD$ ).

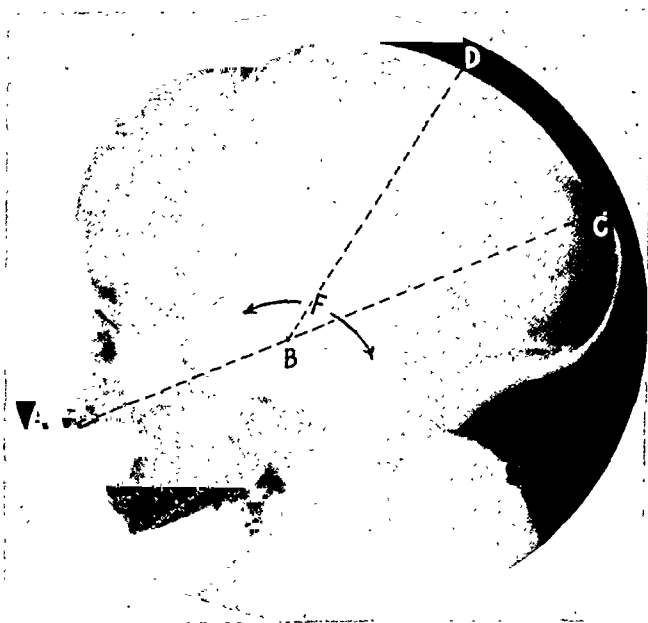


Fig. 9.—Lateral view of an unmolded fetal head delivered by elective cesarean section. Note the obtuse sphenopetrous angle ( $F$ ), and the short sphenoververtical diameter ( $BD$ ), and the short maxillary-vertical diameter ( $AD$ ). The tip of the occipital bone is above the maxillary sphenoccipital line.  $ABC$ , in the molded head (Fig. 8), but in the unmolded example (Fig. 9), it is situated at the level of this line.

parietal bones may be pushed forward or backward by unequal pressure applied at either the frontal or occipital regions of the head.

3. There is a definite decrease in the occipitofrontal diameter (*AE*, Fig 7).

4. The position of the posterior-superior angle of the frontal bone is fairly constant in molded and unmolded heads although there is slight elevation and slight backward displacement (*B*, Fig. 7).

5. The tip of the occipital bone is displaced slightly forward, but the more important change refers to the elevation of the tip in molded heads as compared to the cesarean section group (*D*, Fig. 7).

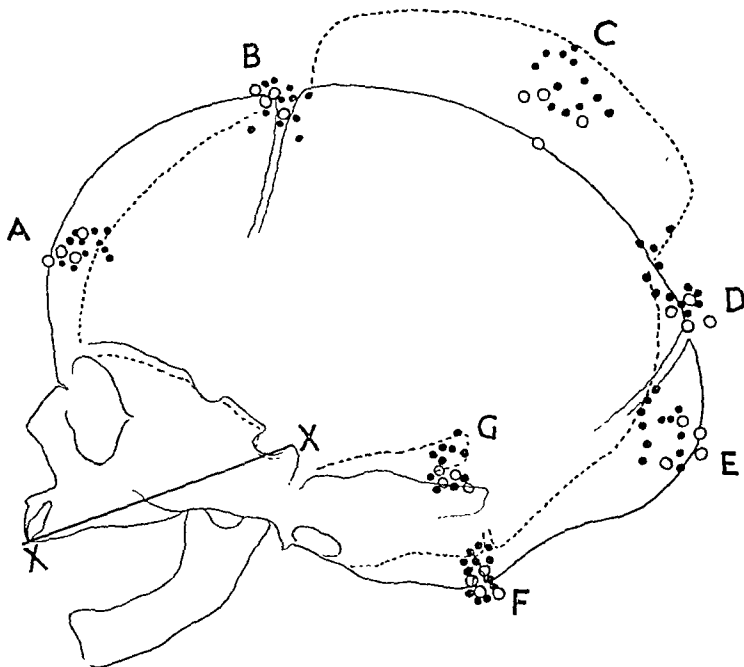


Fig. 7.—This composite diagram shows the variations in the positions of the following landmarks on the circumference of the fetal head. (*A*) the frontal origin of the occipital-frontal diameter, (*B*) the posterior-superior angle of the frontal bone, (*C*) the midpoint of the parietal bone along the vault of the skull, (*D*) the tip of the occipital bone, (*E*) the occipital origin of the occipitofrontal diameter, (*F*) the posterior-inferior extremity of the occipital condyles, (*G*) the posterior extremity of the superimposed petrous portion of the temporal bone. The films were compared by superimposing the tips of the dorsum sellae in each film. The upper incisor tooth on one film was adjusted until it coincided with a line joining the dorsum sellae and the upper incisor tooth on the other film (line *XX'*). The outline of the molded head and the unmolded example were traced from the case studies illustrated in Figs. 8 and 9. Molded heads, solid dot •; unmolded heads, small circle ○.

6. The tips of the occipital condyles are also elevated and this change may be associated with the elevation of the tip of the occipital bone (*F*, Fig. 7).

7. There is elevation of the distal aspects of the superimposed petrous portion of the temporal bones (*G*, Fig. 7) which reduces the size of the sphenopetrous angle.

8. The variations listed in five, six, and seven suggest that elevation of the entire base of the skull behind the sella turcica may occur in molded heads.

Before attempting to describe these changes in detail, it is of interest to determine the differences between these observations as listed and

on the backward and forward movement of the occipital plate at the occipital hinge; bending of the bones is secondary to this and is, of course, a very necessary accompaniment."

Many years ago Ballantyne recorded important observations on head molding in a treatise on *Ante-Natal Pathology and Hygiene*. He questioned the concept that the occipital plate actually demonstrates the great mobility during labor which can be elicited in the newborn or stillborn infant. However, he also believed that "there is no molding of the basi cranii during labor, and it is fortunate for the fetus that there is not."

It will be observed that these descriptions differ chiefly in regard to the question of changes in the base of the skull.

The shift and displacement of anatomical landmarks suggested from the study of Fig. 7 are shown to advantage by the comparison of lateral and anteroposterior roentgenograms of a markedly molded head and a well-formed unmolded example (Figs. 8, 9, 10, 11). These two examples were chosen from the case studies used to construct the composite diagram illustrated in Fig. 7.

The sphenovertical diameter ( $BD$ ) as well as the maxillary-vertical diameter ( $AD$ ) are markedly increased in the molded head. The increase in these diameters can be caused by two factors: free bending of the parietal bones both in the sagittal and coronal axis, or elevation of the parietal bone; or by a combination of both. The free bending along the vault is apparent in Fig. 8 and the difference in contour of the parietal bones in molded and unmolded heads in the coronal axis may be observed by comparing Figs. 10 and 11. Elevation of the entire parietal bones can occur only through separation at the lateral suture lines at the base of the skull and separation to a considerable degree is shown in Fig. 10. Little attention has been directed to the lateral suture lines, and, in most obstetrical texts, diagrams devised to show the effects of molding fail to indicate separation at this point. Marked separation of the lateral suture line is not observed in fetal heads showing slight evidence of molding. It would seem that separation at this suture line occurs chiefly in extreme examples of molding when the stress of labor produces a greater increase in the sphenovertical diameter than can be gained by free bending of the parietal bones along the vault of the skull. Likewise unequal separation occurs at this suture line if the vault of the skull is displaced forward by unusual pressure applied to the occipital region of the head (Fig. 1).

The reduction in length of the occipitofrontal diameter is caused by several factors. First the frontal bone itself may be flattened by direct pressure if the bone is not too calcified (compare Fig. 1 and Fig. 8). The bending of the parietal bones along the sagittal suture line causes a slight reduction in width of each parietal bone which slightly reduces the occipital-frontal diameter. Free bending and forward displacement of the occipital plate reduces it still further.

#### B. CHANGES IN THE BASE OF THE SKULL CAUSED BY MOLDING AND INCREASED BY COMPRESSION

The study of the composite diagram illustrated in Fig. 7 suggested that elevation of the entire base of the skull behind the sella turcica may occur in molded heads. These changes may be observed in the

is more rigid and, although it becomes bent to a certain extent, confines itself chiefly to the role of moving backward and forward on the occipital hinge carrying with it the rest of the vault. The vault of the skull is plastic as a whole and can, within limits, change shape in most directions, but alterations in the shape of the head are chiefly dependent

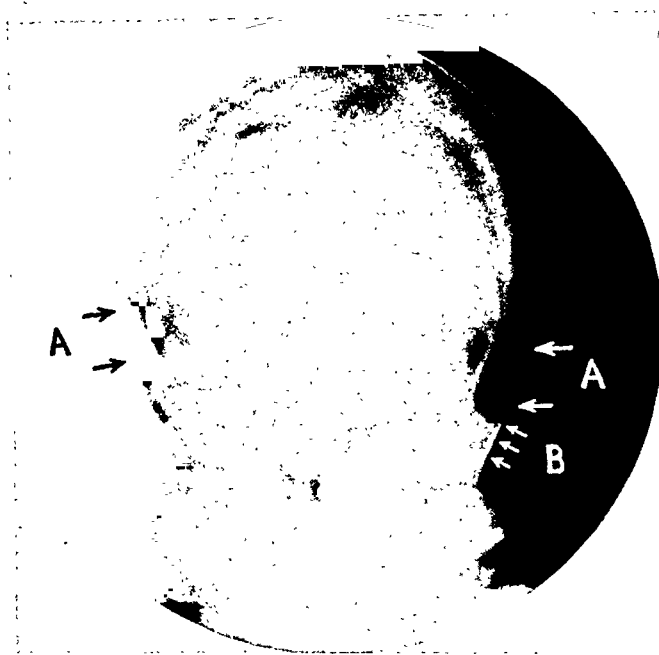


Fig. 10.—Anteroposterior view of case study in Fig. 8. Note the separation of the lateral suture (A) and the vertical position of the greater wing of the sphenoid and squamous portion of the temporal bone (B).



Fig. 11.—Anteroposterior view of case study in Fig. 9. The lateral suture is closed (A). The slope of the greater wing of the sphenoid and squamous portion of the temporal bone (B) is less vertical than in Fig. 10. In Figs. 10 and 11 observe the difference in curvature of the parietal bones in the coronal plane,





Fig. 12.—Lateral view of a stillborn head without compression. (See also Fig. 13.)

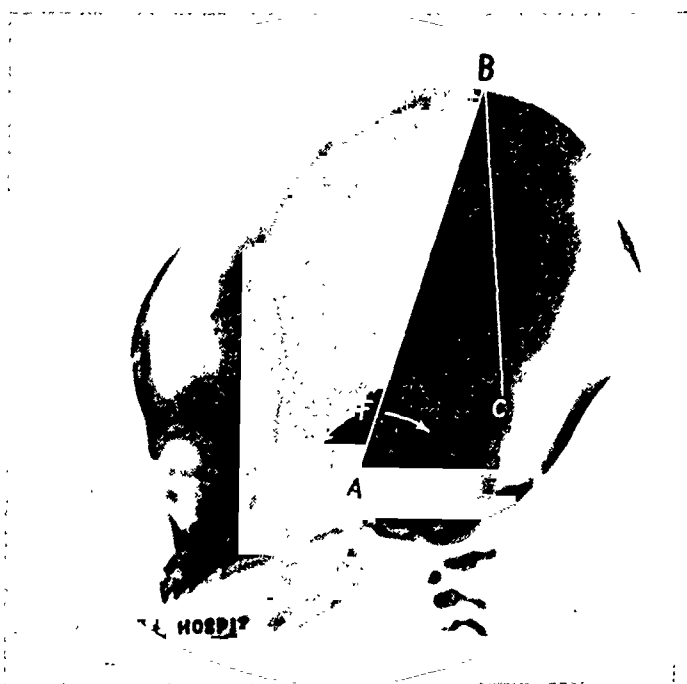


Fig. 13.—Lateral view obtained after compression was applied to case study shown in Fig. 12. Compression causes an increase in the sphenovertebral diameter,  $AB$ , but the midpetrovertical diameter,  $BC$ , remains approximately constant. The sphenopetrous angle,  $F$ , is made more acute by compression.

base of the skull to advantage in the lateral views shown in Figs. 8 and 9. In the unmolded head (Fig. 9), the base of the skull is flat and the sphenopetrous angle is obtuse. In the molded head (Fig. 8), this angle ( $F$ ) is quite acute and the petrous portions of the temporal bone appear to protrude into the posterior-inferior aspect of the cranial cavity. The entire occipital region, including the occipital condyles and the occipital plate is elevated. As a result, the tip of the occipital bone is elevated from one-half to one centimeter above the maxillary-sphenoccipital line (Figs. 8 and 9, line  $ABC$ ). In the postnatal period, the tip of the occipital bone descends still further and in the adult is at an even lower level to the maxillary-spheno-occipital line.

Elevation of the occipital plate is associated with elevation of the occipital condyles and the superimposed edges of the petrous portion of the temporal bone. The degree of elevation of these two landmarks at the base of the skull is indicated in the skull outline of these two heads illustrated in Fig. 7. Elevation of the occipital plate is dependent upon bending at the apex of the sphenopetrous angle or within the occipital condyles (see Fig. 6 and Figs. 8 and 9, angle  $F$ ). The sphenopetrous angle is more acute in the molded head.

With molding, changes may occur in the slope of the squamous portion of the temporal bone and the greater wing of the sphenoid bone. It becomes more vertical in molded heads and flares outward in the unmolded forms, indicating that molding decreases the diameter between the crests of these bones in the region of the lateral suture lines (Figs. 10 and 11). This again demonstrates a change in the bones at the base of the skull.

It is difficult to demonstrate basal changes in the average newborn head because in the average case the change is slight and even in marked cases restitution occurs almost immediately. We, therefore, employed a method of towel compression to simulate the squeeze effect of labor and so increase the changes observed and described in the case studies illustrated in Figs. 8 to 11. For safety, the method was first used upon a stillborn infant. We subjected the head to a considerable compression using the method illustrated in Fig. 3. The lateral roentgenograms shown in Figs. 12 and 13 were obtained. It will be observed that there is a marked diminution in the size of the sphenopetrous angle ( $F$ ). There is a slight increase in the length of the sphenovertical diameter ( $AB$ ) as would be expected. It is interesting to observe that the midpetrovertical diameter ( $BC$ ) remains fairly constant indicating that elevation of the condyles has prevented an increase in this diameter as the petrous portions of the temporal bone are elevated also.

When the outline of the vault is traced on copying paper on one film and is compared with the outline of the head in the compression film, it is noted that the entire vault in the compression film has been deflected forward to a definite extent, approximately one-half centimeter (Fig. 14). This diagram also shows that the midpetrovertical diameter



Fig. 16.—Lateral view obtained after compression was applied to case study shown in Fig. 15.

A comparison of these views, Figs. 15 and 16, show changes which are almost identical to those noted in the stillborn case study of Figs. 12 and 13. In Fig. 16 compression has caused an increase in the length of the sphenovertebral diameter *AB*, and the sphenopetrous angle, *F*, is more acute than in the resting lateral Fig. 15. In both views, the midpetrovertebral diameter *CB* is fairly constant and has not been affected by compression.

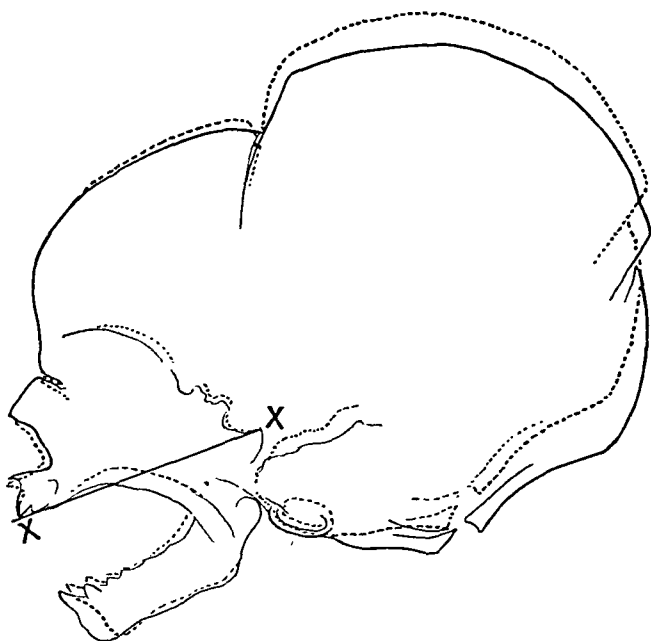


Fig. 17.—Superimposed outlines of the lateral views illustrated in Figs. 15 and 16 show the degree of change in the vault and the skull base caused by compression. Solid outline, resting lateral view. Dotted outline, compression lateral view.



Fig. 14.—The changes caused by compression in a stillborn infant. The dotted line illustrates the effect of compression. These films were compared by superimposition of the line XX joining the incisor tooth and the tip of the dorsum sellae (case study of Figs. 12 and 13). The degree of elevation of the occipital region in the compression case (dotted outline) as compared to the resting lateral (solid outline) indicates the amount of bending which occurred behind the sella turcica.



Fig. 15.—Lateral view of the living fetal head obtained one hour after delivery.

## B. THE MECHANISM OF LOCKING AT THE CORONAL AND LAMBDOIDAL SUTURES

Examination of the suture lines and the hinge action of the occipital plate in stillborn infants after the scalp is reflected shows several interesting facts. When pressure is applied to the parietal bones laterally, the median sagittal suture closes and all transverse diameters are slightly reduced in size. The diameter between the anterior-inferior borders of the parietal bones at the anterior lateral fontanel (the anterior-inferior biparietal diameter, see Fig. 5) is narrower than the bifrontal diameter.



Fig. 18.—Locking mechanism as demonstrated on the stillborn infant after scalp has been reflected. When pressure is exerted between the parietal bones a form of locking occurs at the junction of the middle and lower third of the coronal suture (see arrow).

The posterior edge of the frontal bone along the coronal suture, therefore, crosses the anterior edge of the parietal bones on either side as these lines converge toward the anterior fontanel (see Fig. 18). As a result, an effective locking occurs at the junction of the lower and middle third of the coronal suture which limits to a great extent any forward displacement of the parietal bones. This observation may explain the fairly constant position of the posterior-superior angle of the frontal bones for both the molded and unmolded heads as revealed by Fig. 7B. For this reason, it is unusual to find any overlapping along the coronal suture except to a very slight extent at the posterior-superior angle of the frontal bones. The apparent overlapping of the parietal and frontal bones is not true overlapping but is brought about

is not increased in the compression outline because the posterior aspects of the base of the skull, i.e., the occipital condyles and the petrous portion of the temporal bones, are elevated by the compression.

It seemed sufficiently important to attempt to produce these findings in the head of a living newborn infant, and after due consideration it seemed that no harm would result from the use of gentle towel compression. As a matter of fact, the mobility at the base of a well-molded fetal head, especially in the negro race, can be demonstrated immediately after birth by hand pressure between forehead and occiput. Quite distinct movement in the bones of the skull base below the lateral suture lines can be appreciated. A compression binder was used on nine living infants. Although the changes described above were noted in all these cases, the use of the towel obscured landmarks necessary for the proper positioning of the head for x-ray examination. Perfect lateral views suitable for illustration purposes were obtained in only two instances and one of these examples is shown in Figs. 15, 16, and 17. These films show compression changes in the skull base and cranial vault which are identical with the changes observed in the stillborn case study illustrated in Figs. 12, 13, and 14, and in living newborn babies immediately after delivery (Figs. 8 and 10).

It will be observed that the midpetrovertical diameter is not increased by towel compression in a living child quite similar to the situation created by compression in the stillborn infant (Figs. 12, 13, and 14). This is an important observation. It suggests that in average molding the tentorium which is attached to the petrous portion of the temporal bone will not show increased tension. It has always been assumed that, in molding, considerable tension is placed on the tentorium cerebelli by elevation of the vault of the skull. It would seem that increased tension in the tentorium may not occur in the average case because the petrous portion of the temporal bone elevates and so prevents tension in spite of the fact that the sphenovertical diameter is increased in length.

From the study of all these examples, the nature of molding seems to be as follows:

1. There is an increase in the sphenovertical and to a lesser extent in the maxillary-vertical diameters.
2. The sphenopetrous angle is made more acute through bending at the suture line existing between the sphenoid and basiocciput.
3. The occipital condyles are elevated.
4. The petrous portions of the temporal bone are elevated.
5. The occipital plate is elevated.
6. The vault of the skull, i.e., the occipital and parietal regions, is displaced forward.
7. The midpetrovertical diameter is constant because, with compression, the base of the skull behind the sella turcica is elevated and thereby maintains a constant length to this diameter.

application of forceps was made to a stillborn infant after the scalp had been reflected. As soon as slight pressure was exerted by the forceps in the biparietal diameter, effective splinting of the cranial vault occurred and as pressure was increased, the effectiveness of the locking mechanism at the coronal and lambdoidal sutures became more apparent. With the head thus held, the vault as a whole becomes relatively immobile and considerable external pressure is required to depress any single bone. During labor, between contractions, the occipital plate may underride the parietal bones at the lambdoidal suture lines, and in front, the frontal bones may also slide under the parietal bones. However, with a contraction, the constriction forces which reduce the biparietal diameter bring about this mechanism of locking at the coronal and lambdoidal suture lines which prevents and may even reduce overlapping and so protects the cranial contents from injury. It is evident that after this locking mechanism has occurred no further molding of the vault by overlap of bones can take place. Further molding with diminution of the occipitofrontal and increase of the sphenovertical diameters does, however, take place as the labor goes on and the compression forces continue to act. The explanation of this is to be found in a study of the base of the skull. It has hitherto been believed and taught that the base of the skull was rigid and underwent no molding. Studies of our roentgenograms disprove this.

#### CONCLUSIONS

This investigation draws attention to changes in the base of the skull, a region hitherto considered unaffected by the stress of labor. To demonstrate and magnify these changes, a compression binder was used to simulate the squeeze of labor. Certain cephalic diameters have been described which are directly affected by these changes. During extreme molding the midpetrovertical diameter remains constant. We believe this observation is important since it would infer that it acts in a protective manner to avoid tension on the tentorium cerebelli. This investigation, however, is concerned with a discussion of skull changes rather than with the influence of these changes upon intracranial mechanics. The concept of the mechanism of molding brought out by this investigation is that there is locking of the frontal and parietal bones at the coronal suture, and to a lesser extent, of the occipital and parietal bones at the lambdoidal suture. This mechanism of locking allows bending and displacement in the vault because there are compensating changes in the base. Basal changes consist of elevation of the occipital region with bending at the sphenopectrous angle.

Although this study is a part of the larger problem regarding the question of disproportion between the head and the pelvis, no constructive ideas regarding the estimation of head size have been developed. We believe the changes observed are important enough to report in the hope that the observations may be confirmed by other workers.

by the elevation of the parietal bones which changes the direction of the anterior fontanel from a horizontal to a more vertical plane. This is really pseudo overlapping.

A similar but less effective mechanism of locking occurs at the lambdoidal suture (Fig. 19). In a newborn infant, the occipital plate has a considerable range of movement forward and backward on the occipital hinge which results in overlapping, as the occipital plate is depressed under the posterior free edge of the parietal bones. As soon as pressure



Fig. 19.—Locking mechanism as demonstrated on the stillborn infant after scalp has been reflected. A similar but less effecting form of locking exists at the lambdoidal suture line (see arrow).

is applied laterally to each parietal bone, this range of motion is considerably restricted and in certain heads overlapping can no longer be demonstrated because locking occurs between the parietal and the occipital bones along the lower third of the lambdoidal suture. In fact, as shown in Fig. 5, the base of the occipital plate is wider than the compressed posterior-inferior-biparietal diameter and the occipital plate actually overrides the parietal bones for a short distance just above the posterior lateral fontanel. The free edge of the occipital bone crosses the free edge of the parietal at this point and a form of locking occurs (Fig. 19). As a matter of fact, the significance of locking along these suture lines was not fully appreciated until a cephalic



DR. LEROY A. CALKINS, KANSAS CITY, MO.—Like Dr. Cosgrove, I feel that this is possibly a portentous move in the direction of a truer knowledge of clinical obstetrics. Perhaps it does not make so much difference which one of the 16 types of pelves we are dealing with as it does how the passenger fits into and goes through that pelvis.

Some 20 years ago I made an attempt to solve this particular problem of head molding, at the suggestion of Dr. Litzenberg. I tried to answer the age-old question of whether birth molding is a change in shape only or is, in part, a change in size? I attempted this on the basis of measurements by water displacement, comparing the well-known differences between dead born infants and liveborn infants, as well as the differences between those infants delivered by cesarean section and those delivered after a rather long and difficult labor. My attempts indicated roughly that there were no changes in size, but the measurements were subject to such inaccuracies that I did not publish the observations. I am very glad therefore to see this beginning made by Dr. Moley to prove that birth molding does not involve any change in size but only a change in shape.

Dr. Moley refers rather late in his paper to the protection the infant has against overcompression by forceps application, due to "locking" at both the coronal and lambdoid sutures. That is all very well if the forceps are correctly applied and there is no asynclitism. I think, however, a warning should be sounded that if the forceps happen to be oblique this "locking" might not be so favorable.

DR. BENJAMIN P. WATSON, NEW YORK, N. Y.—What interested me most in this work was the demonstration that molding is not limited to the vertex but that the base of the skull takes part in it. We have always taught that the base of the skull is the fixed portion and that all molding occurs in the vertex. But if you take a stillborn baby and compress the head in the occipitofrontal diameter you will feel very definitely that angulation occurs at the base of the skull. It is just like a hinge. That to me is a totally new concept and I think is one of the most important things brought out in this paper.

DR. FRED L. ADAIR, CHICAGO, ILL.—Dr. Moley's contribution is important, both for a better understanding of the physiology of labor so far as the fetus is concerned, and also with reference to the fetal pathology which results from the abnormal types of labor. We should recognize, however, that we may have compression of the head without molding; although we never have molding without compression. The child's head is not a perfect sphere nor the birth canal a perfect cylinder, which makes considerable difference in the causation of head injuries.

DR. MOLOY (closing).—I wish once more to emphasize that in any routine series it is now rare to find extreme molding resulting from a delivery during which a definite degree of disproportion was overcome by flexion and molding. It is in this type of case that the vault and especially the base of the skull show the changes described in this report. At the present time, cesarean section is employed frequently in borderline cases of disproportion as in the case study illustrated in Figs. 15 and 16. Here the degree of disproportion was great enough to consider this method of delivery several times during the long labor. This case was the one which showed marked changes in the base of the skull when compression was used.

The author wishes to express his appreciation to Dr. Ross Golden and Dr. Caffey of the Department of Radiology of Presbyterian Hospital and Babies' Hospital for their interest in this study. The interest and technical assistance of Miss Piper and Mr. Watts are also deeply appreciated. The author is indebted to Miss Powers and Mrs. Fries, supervisors of the Delivery Room and the Nurseries of the Sloane Hospital for Women for their cooperation in these studies.

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#### DISCUSSION

DR. SAMUEL A. COSGROVE, JERSEY CITY, N. J.—It seems to me that the new concept of molding which Dr. Moloy has presented consists essentially in his statement that the bones of the base of the skull partake in a change in relationships, due to molding, in addition to the changes of the calvarium, which have long been recognized. He has presented certain evidence in support of this concept.

I hope as he does that his observations will be confirmed by other workers, for I am afraid that the evidence presented, and that is all which we have at this time to go on, might fail to be strongly convincing. For instance, in the two films comprising Figs. 1 and 2, the sphenopetrous angle is just about the same immediately after birth and eleven days later. Had much distortion originally existed, is it not reasonable to suppose that it would have changed in eleven days, as that of the calvarium so plainly has?

In Figs. 8 and 9 are pictures of *different* heads. Contours of the same parts may well vary in different individuals without relation to the effects of compression. In Figs. 1 and 2, tracings of the contours of the bones themselves do not coincide in the two pictures. This suggests that slight changes in the angle at which the two films were taken may also account for the apparent difference in relationship. In Figs. 12 and 13, tracings of the contours of the bones in the two films almost coincide, the difference being too small to be significant. In Figs. 15 and 16, the apparent difference is obtained by superimposing an arbitrary artificial line in the two films. When the *contours of the bones* are superimposed, the difference in relation is much less apparent.

I have, however, no desire to be hypercritical, for I think his work has most important clinical implications. If true, it means: (1) that such basilar molding occurs only in relatively high degrees of disproportion; (2) that it is the *last* part of total molding to take place; (3) that it is the slowest and most difficult part of molding; (4) that engagement cannot be complete before it has been accomplished; (5) that this takes lots and lots of time; (6) that therefore arbitrary limitation of time for the duration of the second stage are invalid; (7) that the accomplishment of complete molding, and not the complete dilatation of the cervix, becomes the *most important criterion* for the proper exhibition of artificial interference.

If there can be universal realization of these implications of Dr. Moloy's work, and if thereby current premature and pernicious interference can be reduced, then his contribution constitutes a service which the Society may well hail as of the highest value.

TABLE I. CLASSIFICATIONS OF THE OBSTETRIC PELVIS BASED ON SIZE, MENSURATION, ETIOLOGY, PATHOLOGY AND MORPHOLOGY

| YEAR   | AUTHOR                   | SEX        | PELVIC TYPES      |              |              |                |                   |                     |                            |
|--|--------------------------|------------|-------------------|--------------|--------------|----------------|-------------------|---------------------|----------------------------|
|  |                          |            | 1                 | 2            | 3            | 4              | 5                 | 6                   | 7                          |
| 1701   | Deventer                 | F.         | Too large         | Round        |              | Too small      |                   | Narrow              |                            |
| 1746   | Baudelocque              | F.         |                   |              |              |                |                   |                     |                            |
| 1752   | Smellie                  | F.         |                   |              | Oval         |                |                   |                     |                            |
| 1825   | Stein                    | M.F.       |                   | Round        |              |                |                   |                     |                            |
| 1830   | Weber                    | M.F.       |                   | Round        | Oval         |                |                   | Transverse ellipse  | A.P. ellipse<br>4-sided    |
| 1851   | Michaelis                | F.         |                   |              |              |                | Triangular        |                     |                            |
| 1861   | Litzmann                 | F.         | Justo major       | Normal       |              |                | Heart shaped      |                     |                            |
| 1866   | Turner                   | M.         |                   | Mesatipellic |              |                | Wedge shaped      |                     |                            |
| 1889   | Schauta                  | F.         | }                 |              |              |                |                   | Contracted          |                            |
| 1898   | Tarnier-Budin            | F.         |                   |              |              |                |                   | Platypellic         | Dolichopellic              |
| 1900   | Breus-Kolisko            | F.         |                   |              |              |                |                   |                     |                            |
| ETIOLOGIC ANOMALIES AND DISEASES OF PELVIS, SPINE, OR FEMURS |                          |            |                   |              |              |                |                   |                     |                            |
| GENERALLY CONTRACTED   |                          |            |                   |              |              |                |                   |                     |                            |
| 1903   | Williams                 | F.         | Justo major       | Female       |              |                |                   |                     |                            |
| 1913   | DeLee                    | F.         |                   |              |              |                |                   |                     |                            |
| 1933   | Caldwell-Moley<br>(Todd) | M.F.<br>F. |                   | Gynecoid     | →1942        | Typical        | Funnel<br>Android | Flat<br>Platypellic | Transversely<br>Anthropoid |
| 1935   | Thoms                    | F.         |                   | Round        | Female oval  |                |                   |                     |                            |
| 1936   | Stander                  | F.         | Justo major       | Female       |              | Justo minor    | Male, funnel      | Simple flat         | Anthropoid                 |
| 1938   | Thoms                    | M.F.       |                   | Mesatipellic | Brachypellic |                |                   | Platypellic         | Anthropoid                 |
| 1939   | DeLee                    | F.         |                   | Gynecoid     | Android oval |                |                   | Platypellic         | Dolichopellic              |
| 1941   | Stander                  | F.         | Gynecoid<br>large | Mesatipellic |              | Gynecoid small | Android           | Platypellic         | Anthropoid                 |
|  |                          |            |                   |              |              |                |                   | Platypellic         | Dolichopellic              |

# CLASSIFICATION OF THE OBSTETRIC PELVIS BASED ON SIZE, MENSURATION, AND MORPHOLOGY\*

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SIZE has been the criterion most generally employed by obstetricians for dealing with the obstetric pelvis regardless of the underlying etiology, pathology, or morphology. Mensuration, through internal and external pelvimetry, has supplied the means for classification. The present clinical results have been attained on this basis.

The roentgen ray techniques have provided information as to morphology and have made x-ray pelvimetry possible for the determination of size and have provided a knowledge of labor mechanisms. The close interrelationship of all of them has been established. Further advance and greater precision in obstetric practice through the utilization of this knowledge are to be expected. It is evident that the first step in this direction is a provision for morphology in pelvic classification. Two morphologic classifications have been recently proposed and dissimilar methods of radiographic study are employed by their advocates. Morphology is determined in different ways. It is the purpose of this communication to consider these classifications, as well as the methods of diagnosis, and to outline a method of approach which combines the best features of each.

## HISTORICAL

Classifications of the obstetric pelvis have been under discussion for the past 241 years. Van Deventer is credited with the first classification in 1701. Pelvic mensuration was employed by Baudelocque, Smellie, Michaelis, and Litzmann. Anatomists and anthropologists have long employed morphology as a basis of classification as illustrated by the work of Stein, Weber, and Turner. Thereafter, etiologic and pathologic classifications were advanced by Schauta, Tarnier-Budin and Breus and Kolisko. In this country, Williams in 1903, provided a classification based on a combination of the earlier concepts. He was supported in his views by DeLee. In the recently proposed morphologic classifications, Thoms advocates the study of form by means of mensuration and the pelviscope, whereas Caldwell and Moloy employ direct observation of an undistorted image in the precision stereoscope. Very recently (1941), Stander has proposed a combined etiologic and morphologic classification. In the main, discussion has revolved around seven pelvic types, as summarized in Table I.

\*Read, by invitation, at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.

†Dr. Steele died June 18, 1942.

Thoms has popularized the centimeter grid technique for securing an image of, and measuring the superior strait. The plane of the anteroposterior diameter of the inlet has been obtained by means of external anatomic landmarks, and the grid has been exposed in an inclined posi-

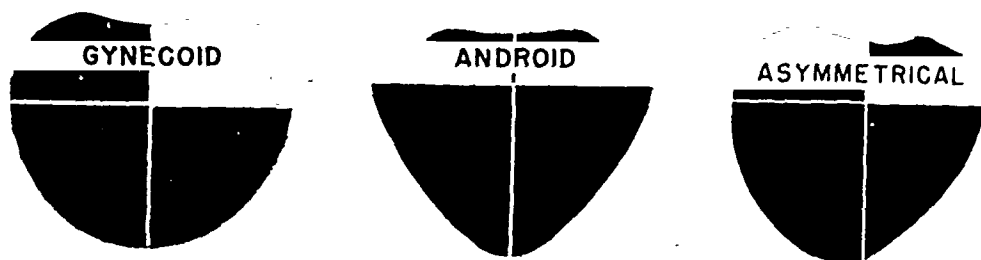


Fig. 2.—Relationship of the A-P diameter to the transverse is not a true index of form.

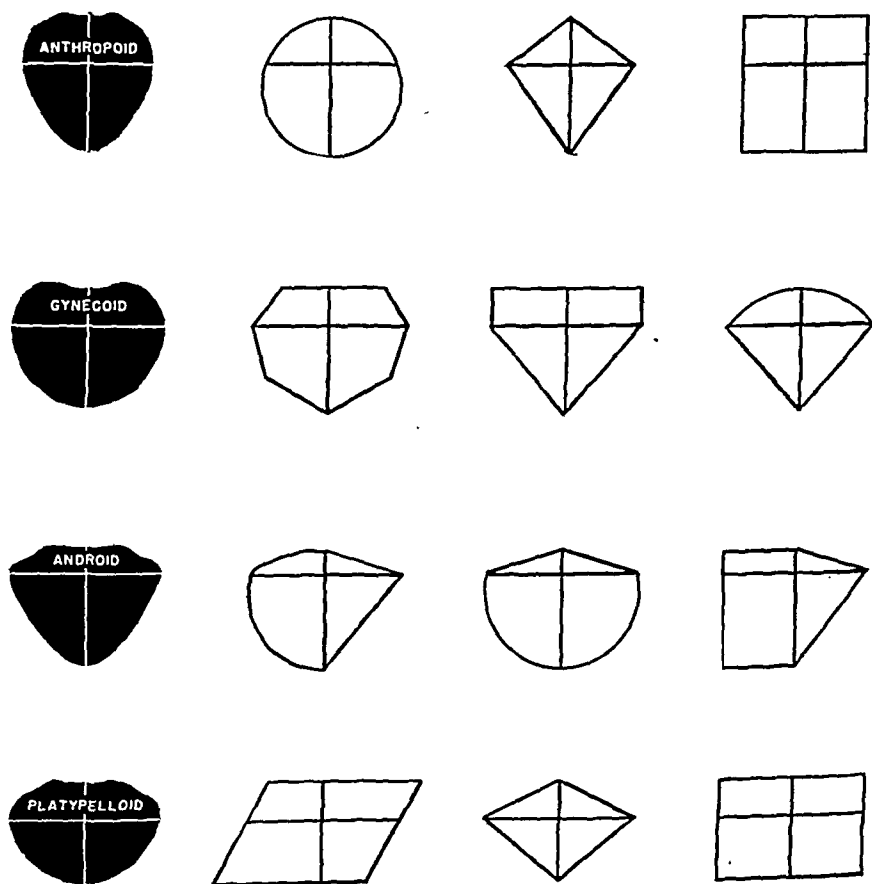


Fig. 3.—Anteroposterior and transverse diameters are not a true index of morphology, nor of volumetric capacity, at the pelvic brim.

tion. This has resulted in unequal distortion of the anteroposterior and transverse diameters of the inlet because the transverse diameter is often as much as 2 cm. below the anteroposterior diameter, as has also been pointed out by Snow. In a study of dried pelves, employing the original

The etiologic classifications, including that of Williams, divide all pelvis into normal and contracted forms. Eliminating the rare pathologic forms and comparing the remainder of the pelvis, which constitute about 99 per cent of all pelvis, one finds that about 85 per cent are normal and adequate, and 15 per cent contracted. In either group, classification according to pelvic morphology can be carried out as indicated in Fig. 1. The term growth variants long employed by anthropologists is all inclusive as to the etiologic factors, namely, growth hormones, sex hormones, nutrition, retardation, mechanical stresses, etc. The etiologic role of these has not been clearly established, but they probably influence size and morphology.

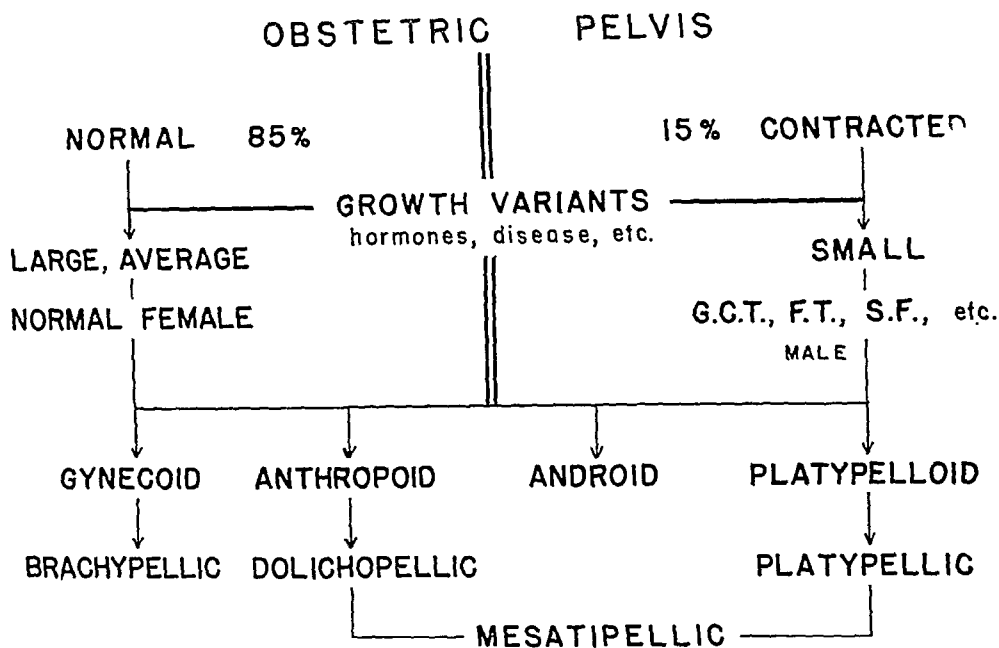


Fig. 1.—Showing how growth variants influence size and morphology of the obstetric pelvis.

#### RECENTLY PROPOSED MORPHOLOGIC CLASSIFICATIONS

Thoms has proposed a classification based upon morphology of the pelvic brim. A study of distorted roentgen ray images has provided the background for his classification. Thoms describes only four types. As a specific criterion to determine morphology, he uses a simple relationship of the anteroposterior and transverse diameters and has regarded this as an adequate index of form, which is essentially the method proposed by Turner in 1866. Omission of the android type of inlet is especially noteworthy.

The relationship of the anteroposterior diameter to the transverse diameter of the inlet is not always a true index of form, as shown in Fig. 2. The anteroposterior and transverse diameters are the same in all three figures. It is manifest that this index fails to show (1) shortening in the posterior sagittal diameter; (2) narrowing in the forepelvis; which serve to distinguish the well-known pelvic types, namely, male and female; and (3) asymmetry. Calculation of pelvic capacity on the basis of these diameters is also inaccurate, as indicated in Fig. 3.

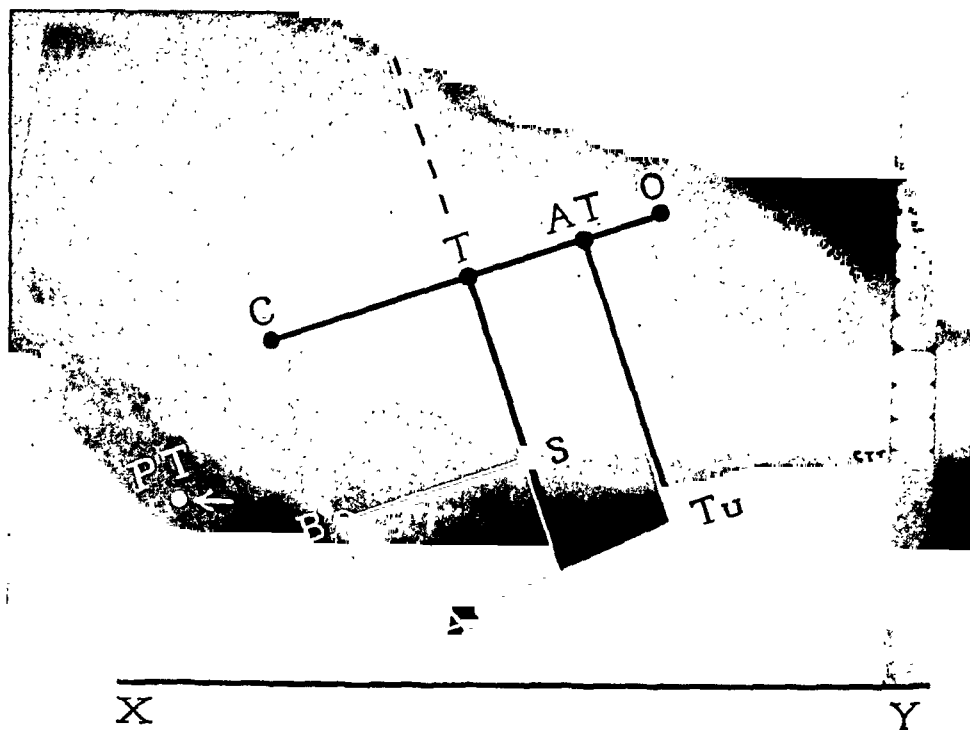


Fig. 4.—Lateral film. Base line X-Y is drawn perpendicular to the centimeter rule at the lower tip. Anteroposterior diameter of the inlet C-O is drawn in the plane of the ileopectineal lines projected on the sacrum and symphysis. T-S is a perpendicular to the inlet drawn through the bases of the ischial spines; and provides the plane of the transverse diameter of the inlet. If continued upward, it passes through the iliac crests. A coronal plane in the transverse diameter divides the entire pelvis into anterior and posterior segments. C-T and T-O are the posterior and anterior sagittal diameters. Points T, AT, PT, S and Tu, mark the vertical heights of their respective transverse diameters (shown in Fig. 5) from base line X-Y.

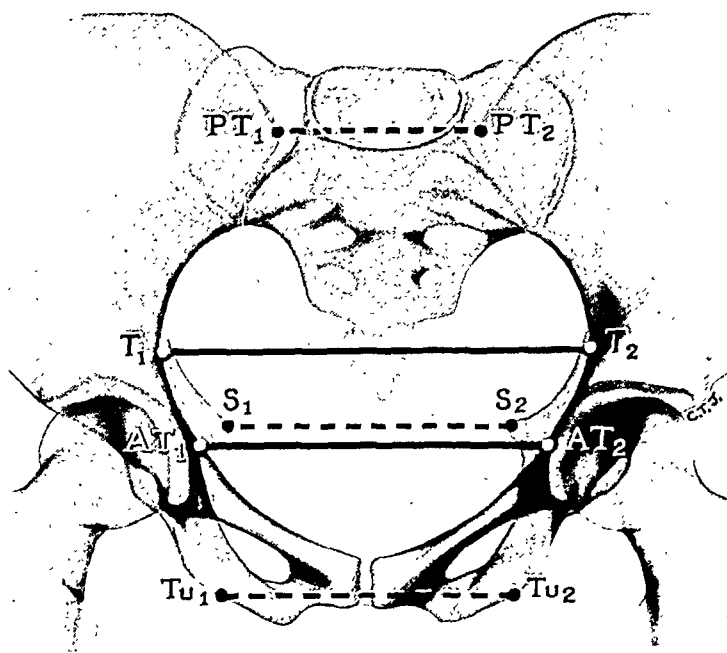


Fig. 5.—Frontal film. Showing the transverse ( $T_1-T_2$ ) anterior and posterior transverse ( $AT_1-AT_2$ ,  $PT_1-PT_2$ ) diameters, interspinous ( $S_1-S_2$ ), and intertuberos ( $Tu_1-Tu_2$ ) diameters. These can be measured on distorted scales corresponding to their vertical heights, T, AT, PT, S, and Tu, obtained from the lateral film (Fig. 4).

technique of Thoms, an error slightly in excess of a centimeter was found in 3 out of 4 pelves in the transverse diameter, as shown in Table II. This error has been eliminated in Thoms' newer technique in which the centimeter grid is placed parallel to the film and in the plane of the iliopectineal lines.

A comparison of data published by Thoms shows a difference of 0.5 cm. between the anteroposterior and transverse diameters in the predominant or average female pelvis, and is very much below the difference of 2.0-2.5 cm. recorded by other authors, as shown in Table III. The potential error in technique demonstrated experimentally may explain the variations in measurements of the predominant pelvic type reported by Thoms. Strict adherence to the sole mensurational criterion employed also probably explains the failure to recognize the android or male type of inlet recognized by most anthropologists, anatomists, and some obstetricians.

TABLE II. TRANSVERSE DIAMETER IS DISTORTED WHEN THE CENTIMETER GRID LIES IN THE PLANE OF THE C.V. DIAMETER AND PARALLEL TO X-RAY FILM

| DRIED PELVES  | A    |        | B    |        | C    |        | D    |        |
|---|------|--------|------|--------|------|--------|------|--------|
| DIAMETERS   | C.V. | TRANS. | C.V. | TRANS. | C.V. | TRANS. | C.V. | TRANS. |
| Cm. $\left\{ \begin{array}{l} \text{Actual} \\ \text{Grid} \end{array} \right.$ | 11.0 | 13.6   | 10.7 | 13.2   | 10.8 | 14.0   | 11.0 | 12.9   |
|   | 11.0 | 13.0   | 10.7 | 12.0   | 10.8 | 12.8   | 11.0 | 11.8   |
| Difference  | 0.0  | 0.6    | 0.0  | 1.2    | 0.0  | 1.2    | 0.0  | 1.1    |

TABLE III. COMPARISON OF ANTEROPOSTERIOR AND TRANSVERSE INLET DIAMETERS OF THE AVERAGE FEMALE PELVIS

| DIAMETER (CM.)             | STANDER<br>DE LEE | JARCHO | TODD         | CALD-<br>WELL-<br>MOLOY | STEELE | THOMS        |
|----------------------------|-------------------|--------|--------------|-------------------------|--------|--------------|
| Anteroposterior            | 11.0              | 11.0   | 10.8         | 11.2                    | 11.0   | 11.5-12.25   |
| Transverse                 | 13.5              | 13.5   | 13.7         | 13.2                    | 13.0   | 12.0-12.75   |
| Difference                 | 2.5               | 2.5    | 2.9          | 2.0                     | 2.0    | 0.5          |
| Predominant pelvic<br>type | ← female →        |        | ← gynecoid → |                         |        | mesatipellic |

The use of a centimeter scale in the lateral film provides accurate measurements of anteroposterior diameters in the sagittal plane of the pelvis and is employed by ourselves (Fig. 4) as well as by Thoms and Caldwell and Moloy.

Caldwell and Moloy have proposed a morphologic classification in which is described four parent forms based on a study of dried pelves. They divide the pelvic inlet into an anterior and posterior segment and provide for combinations of these segments so that 14 forms result. In their total material these forms are divided equally into pure and mixed types, and this division has been observed in the pelves studied at Cornell. They employed the precision stereoscope primarily for a study of morphology and secondarily for mensuration. The stereoscopic technique has been approved by the Society of American Roentgenologists and has been considered extremely accurate. Difficulty has been experienced by many when using the stereoscope for mensuration.

Caldwell and Moloy have insisted on provision in their classification for the pelvis as a whole, including the brim, midpelvis, and outlet. They



and third sacral vertebrae, as indicated in Fig. 4. It can be measured clinically with the small Williams' pelvimeter by selecting the medial edges of the dimples, or in thin patients, the actual inner margins of the iliac crests at the proper points. X-ray measurement is ordinarily about a centimeter less than the clinical measurement.

This diameter is greater in the female pelvis than in the male as has been pointed out by Jarcho and confirmed by a study of 69 dried pelves in the Cornell University collection. In 34 dried gynecoid pelves, an average measurement of 7.1 cm. was obtained and in 23 dried android pelves, the average was 5.3 cm. as shown in Table IV, a difference of nearly 2 cm. The posterior transverse diameter provides an excellent opportunity for the recognition of the android posterior segment.

#### PROPOSED METHOD OF CLASSIFICATION OF THE PELVIC INLET

The incorporation of the isometric and stereoscopic principles of Thoms and Caldwell and Moloy into a combined technique was prompted in part by the hope that the nomenclature of their classifications could also be combined. The terms, "dolichopellic" and "anthropoid," and "platypellic" and "platypelloid," refer to the anteroposterior ellipse and transverse ellipse respectively as shown in Table I. The terms are synonymous and may be used interchangeably. However, this does not hold for the large intermediate group of pelves, namely, the "mesatipellic" and "gynecoid," and the "brachypellic" and "android" forms; which constitute about three-fourths of the total number, as shown in Table V. These two groups are not isometric judging from the available descriptions. As a matter of fact, as indicated in Table I, the mesatipellic pelvis of Thoms has been placed with the round or female types of other authors, whereas, the brachypellic pelvis is situated with the oval pelves. It has been long recognized that the female pelvis was oval, and Caldwell and Moloy (1942) have agreed to the inclusion of their gynecoid type with this group, so that it now appears that the gynecoid and brachypellic pelves are similar. The mesatipellic is probably a mixed gynecoid with anthropoid. Therefore, care must be utilized when combining both classifications.

TABLE V. INCIDENCE OF PELVIC TYPES

| PELVIC TYPE              | TODD   |      | CALDWELL-MOLOY |      | STEELE |      | THOMS  |      |
|--------------------------|--------|------|----------------|------|--------|------|--------|------|
| Gynecoid                 | 41.4   |      | 50.0           |      | 56.3   |      | —      |      |
| Mesatipellic             | —      |      | —              |      | —      |      | 45.9   |      |
| Brachypellic             | —      |      | —              |      | —      |      | 32.2   |      |
| Android                  | 32.5   |      | 22.5           |      | 19.6   |      | —      |      |
| Total                    |        | 73.9 |                | 73.0 |        | 75.9 |        | 78.1 |
| Anthropoid dolichopellic | 23.5   |      | 22.7           |      | 17.0   |      | 18.6   |      |
| Platypelloid platypellic | 2.6    |      | 4.3            |      | 7.1    |      | 3.3    |      |
| Total                    |        | 26.1 |                | 27.0 |        | 24.1 |        | 21.9 |
| Grand Total              | 100.0% |      | 100.0%         |      | 100.0% |      | 100.0% |      |

provide a long list of terms referable to the sacrosciatic notch, sacral curvature, lateral bore, sidewalls, interspinous and intertuberous diameters. Thoms is in agreement on the necessity of considering the pelvis as a whole. From the obstetric viewpoint, it is apparent that a knowledge of the architecture of the canal and outlet is as necessary as that of the brim. Although the method proposed appears cumbersome, at present there is no other way of dealing with this situation.

#### COMBINED ISOMETRIC AND STEREOSCOPIC TECHNIQUE

Experience with the isometric scale principle of Thoms and the stereoscopic technique of Moloy has shown advantages and disadvantages as indicated above. Certain desirable principles of both have been retained in a combined technique described elsewhere. Identical positioning of the patient has facilitated joint workup of the lateral and frontal films. Anteroposterior and sagittal diameters as well as the vertical heights of transverse diameters can be obtained from the lateral film, as shown in Fig. 4. The latter are of value in measuring transverse diameters in the frontal films, shown in Fig. 5, on a set of distorted scales. Morphology is studied in the precision stereoscope of Moloy as shown in Figs. 8 and 9.

The anterior transverse diameter recently described by Steele and Javert and the posterior transverse diameter described below are of particular value in detecting the android type of pelvis. This has been substantiated by a study of dried pelvises as well as a large number of patients and their roentgenographic films. Values for this diameter are given in Table IV.

#### POSTERIOR TRANSVERSE DIAMETER

The iliac crests just above the posterior superior spines have depressions or dimples contributing to the formation of the rhomboid of Michaelis. These points represent the projection posteriorly of the linear terminalis of Breus and Kolisko, drawn in the planes of the ileopectineal lines on either side of the pelvic inlet. These lines also traverse the iliac tuberosities.

TABLE IV. AVERAGE MEASUREMENTS OF THE ANTERIOR AND POSTERIOR TRANSVERSE DIAMETERS IN DRIED PELVES

| MORPHOLOGY   | POSTERIOR SEGMENT |                           | ANTERIOR SEGMENT |                          |
|--------------|-------------------|---------------------------|------------------|--------------------------|
|              | NO. OF PELVES     | POST. TRANS. DIAMETER CM. | NO. OF PELVES    | ANT. TRANS. DIAMETER CM. |
| Gynecoid     | 34                | 7.1                       | 34               | 11.6                     |
| Android      | 23                | 5.3                       | 23               | 9.9                      |
| Anthropoid   | 8                 | 7.4                       | 6                | 10.3                     |
| Platypelloid | 4                 | 6.8                       | 6                | 12.4                     |
| Total        | 69                |                           | 69               |                          |

The posterior transverse diameter (or posterior cristal or posterior tuberal), shown in Fig. 5, can be measured on the frontal film between the shadows of the iliac tuberosities. The vertical height is obtained from the lateral film at PT in the horizontal plane of the junction of the second

or decreased by the character of each segment; (4) the android type of inlet is included; (5) the etymology of "gynecoid," "android," "anthropoid," and "platypelloid," is more distinctive, and less cumbersome, than "mesatipellic," "brachypellic," "dolichopellic," and "platypellic."

This approach is aimed at the determination of size and pelvic form, and therefore, combines size, mensuration, and morphology. Radiographically this can be done with a minimum of error by correcting for distortion and providing for accurate linear measurement of all diameters with the combined isometric scale and stereoscopic technique described above.

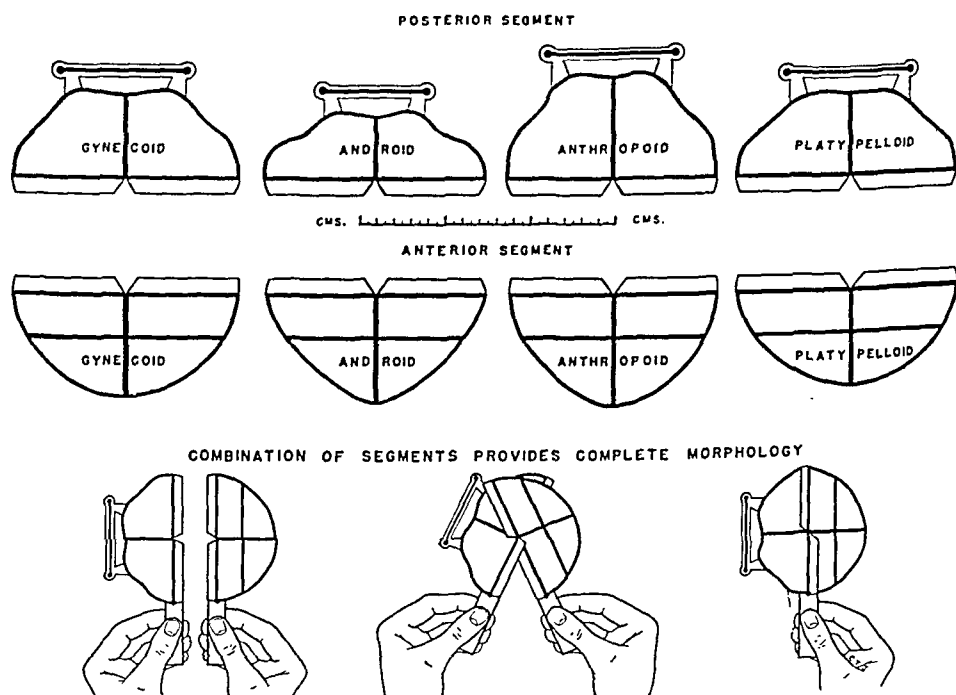


Fig. 8.—Morphology of pelvic inlet is determined according to anterior and posterior segments. These models are for use in the stereoscope as shown in Fig. 9.

It has been recognized that a perpendicular to the anteroposterior diameter of the inlet drawn through the ischial spines passes through the transverse diameter of the inlet. If this perpendicular is projected upward, it also passes through the iliac crests as shown in Fig. 4. Cutting the pelvis in the coronal plane of the transverse diameter divides the entire pelvis into anterior and posterior segments, as shown in Fig. 6. Each segment can be regarded as having gynecoid, android, anthropoid, and platypelloid characteristics. Accordingly, pure and mixed forms can be recognized. Further differentiation of the pelvis as to size, namely; large, average, and small, is included. Etiologic disease can be added in the rare instances as encountered (less than 1 per cent), although a study

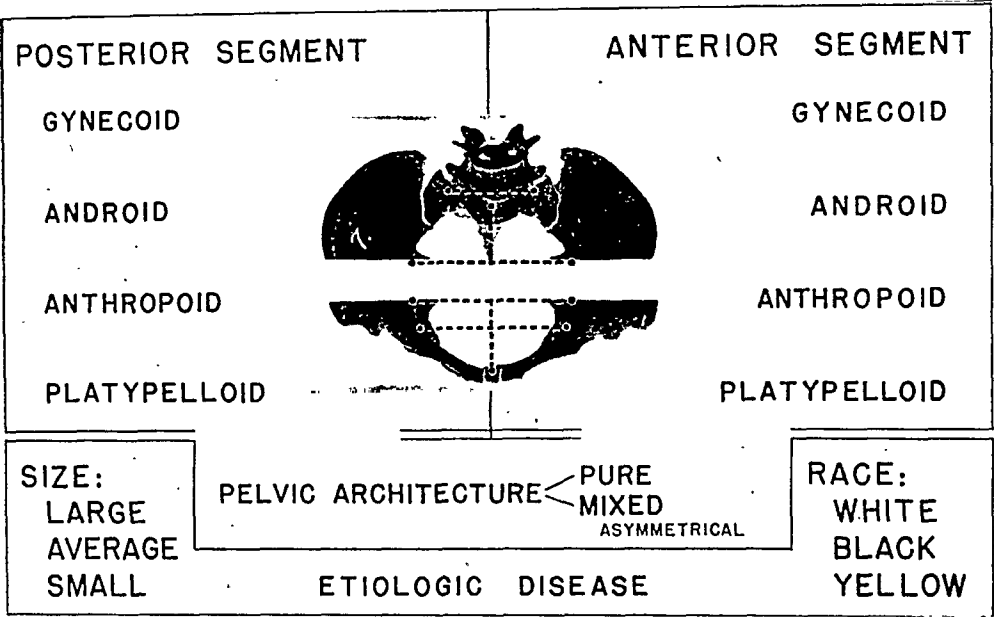


Fig. 6.—Classification of the obstetric pelvis based on mensuration and morphology (clinically and/or radiographically).









|              | POSTERIOR SEGMENT   |           |      |        | ANTERIOR SEGMENT  |          |      | C. O. |
|--------------|---|-----------|------|--------|---|----------|------|-------|
|              | MORPHOLOGY  | POSTERIOR |      | TRANS. | MORPHOLOGY  | ANTERIOR |      |       |
|              |   | TRANS.    | SAG. |        |   | TRANS.   | SAG. |       |
| GYNECOID     |   |           |      |        |   |          |      |       |
|              |   |           |      |        |   |          |      |       |
| pure         |   | 7.5       | 5.0  | 13.2   |   | 11.3     | 6.2  | 11.2  |
| mixed        |   | 7.1       | 5.5  | 12.8   |   | 10.8     | 6.4  | 11.9  |
| ANDROID      |  |           |      |        |  |          |      |       |
|              |   |           |      |        |   |          |      |       |
| pure         |   | 5.9       | 3.7  | 12.9   |   | 10.2     | 6.5  | 10.2  |
| mixed        |   | 6.0       | 3.9  | 13.1   |   | 10.9     | 7.1  | 11.0  |
| ANTHROPOID   |  |           |      |        |  |          |      |       |
|              |   |           |      |        |   |          |      |       |
| pure         |   | 7.5       | 6.0  | 12.2   |   | 10.2     | 6.6  | 12.6  |
| mixed        |   | 7.2       | 6.1  | 12.4   |   | 10.9     | 6.2  | 12.3  |
| PLATYPELLOID |  |           |      |        |  |          |      |       |
|              |   |           |      |        |   |          |      |       |
| pure         |   | 8.2       | 4.8  | 14.3   |   | 12.4     | 5.8  | 10.6  |
| mixed        |   | 8.0       | 4.7  | 14.0   |   | 11.9     | 6.1  | 10.8  |

Fig. 7.—Criteria for classification of the obstetric pelvis combining mensuration and morphology.

The terminology of Caldwell and Moloy has been employed for the following reasons: (1) lack of agreement on the characteristics of the two predominant pelvic types in either classification; (2) the pelvic inlet has been divided into anterior and posterior segments, and pure and mixed forms can be recognized, for the latter constitutes about 50 per cent of the pelves; (3) the obstetric value of a given pelvis is increased

is 85 per cent, leaving 15 per cent as contracted, as shown in Fig. 1. The criterion for this division is a diagonal conjugate of 11.5 centimeters.

TABLE VI. INCIDENCE OF MORPHOLOGY AT THE PELVIC INLET ACCORDING TO SEGMENTS IN 1,000 CASES

| PELVIC TYPE  | POSTERIOR SEGMENT |          | ANTERIOR SEGMENT |          |
|--------------|-------------------|----------|------------------|----------|
|              | NUMBER            | PER CENT | NUMBER           | PER CENT |
| Gynecoid     | 563               | 56.3     | 575              | 57.5     |
| Android      | 196               | 19.6     | 138              | 13.8     |
| Anthropoid   | 170               | 17.0     | 176              | 17.6     |
| Platypelloid | 71                | 7.1      | 111              | 11.1     |
| Total        | 1,000             | 100.0    | 1,000            | 100.0    |

Using a similar standard for comparison, namely, an obstetrical conjugate of 10.5 cm.,\* the incidence of normal and contracted pelves was found to be 70 per cent and 30 per cent, respectively, as shown in Table VII. In other words, x-ray pelvimetry virtually doubled the incidence of contracted forms! On this basis, the gynecoid and anthropoid varieties, constitute 567 of the 700 normal pelves, or 81 per cent, whereas, the platypelloid and android types account for 134 of the 300 contracted group, or 44.1 per cent. Small gynecoid pelves are also frequent. A clinicoradiographic study of 300 pelves has also indicated that an unusually large percentage of contracted pelves were either android or platypelloid in character, showing that size may also be useful clinically in predicted pelvic morphology. Studies now in progress indicate that this can be accomplished with a considerable degree of accuracy.

However, the combined isometric scale and stereoscopic technique illustrated in Figs. 4, 5, 8, and 9, provides an excellent opportunity for the practice of x-ray pelvimetry for the accurate determination of pelvic size, and for direct visual study of morphology, both of which are essential for the proper classification of the obstetric pelvis.

#### CONCLUSIONS

1. Size and morphology constitute the most practical basis for classification of the obstetric pelvis.

2. Mensuration, utilizing x-ray pelvimetry, serves primarily to determine size. Size is an index of morphology in an unusually large percentage of contracted pelves, which are often of the android, platypelloid, or small gynecoid types.

3. X-ray pelvimetry of 1,000 cases has demonstrated that 30 per cent were contracted in contradistinction to an incidence of 15 per cent detected by clinical pelvimetry.

4. Morphology can be most easily and most accurately determined by the direct study of form using the precision stereoscope.

\*This is 1 centimeter less than the average measurement of 11.5 cm. obtained for the obstetric conjugate in 1,000 cases studied radiographically.

of such pelves radiographically has shown that they can be usually classified morphologically.

The criteria for classification using morphology and mensuration of the anterior and posterior segments, based on 1,000 cases, are shown in Fig. 7. In the posterior segment, the morphologic conformation of the superior strait as well as the transverse, posterior transverse, and posterior sagittal diameters are evaluated. With regard to the anterior segment; morphology, and the transverse, anterior transverse and anterior sagittal diameters, are considered. Mensuration is practiced in the stereoscope and on the distorted isometric scales. Ordinarily the measurements vary only 2 mm. with either technique. This approach for consideration of the anterior and posterior segments, according to four parent types, is shown in Fig. 8. These outlines were derived from composite tracings of the inlet made from images in the stereoscope of the four parent pelvic types on glass. The latter was placed in the plane ordinarily employed

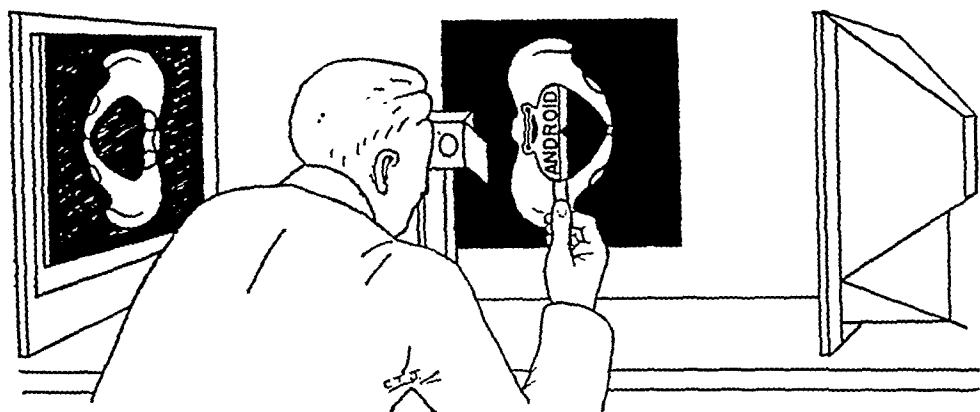


Fig. 9.—Precision stereoscope is used for classification of the inlet using models of anterior and posterior segments shown in Fig. 7, and also for mensuration.

for mensuration. The diagrams were altered slightly to conform to the average measurements for pure types given in Fig. 7. Individual diagnosis of each segment is obtained from undistorted images in the precision stereoscope as shown in Fig. 9. Combination of anterior and posterior segments provides for the recognition of pure and mixed forms at the pelvic brim. The morphology in 1,000 pelves was determined according to segments in the above manner and the incidences are given in Table VI.

#### NORMAL AND CONTRACTED PELVES

The greatest value of mensuration, whether performed clinically or by x-ray, is the determination of pelvic size. Yet, as shown in Fig. 7, mensurational values have some relationship to morphology. Pelves can be divided into normal and contracted forms on the basis of size, mensuration and morphology. Clinically, the incidence of normal pelves

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## DISCUSSION

DR. BENJAMIN P. WATSON, New York, N. Y.—We as obstetricians are under a great debt of gratitude to men such as Thoms, Caldwell and Moloy, and now Steele, who in the past ten or fifteen years have been directing our attention to the variations in the morphology of the female pelvis and their effects upon the mechanism of labor.

There is, of course, nothing new under the sun. These variations were known to the older anatomists and to some of the older obstetricians, such as Berry Hart; but their frequency, their methods of recognition, and their clinical importance were not stressed until our attention was re-directed to them by the investigators mentioned.

The broad classification of Caldwell and Moloy, which places female pelvis in four main types: gynecoid, anthropoid, android, and platypelloid, has received practically universal acceptance, at any rate in English speaking schools of obstetrics. This classification is based upon the shape of the pelvic brim, the relative lengths of its anteroposterior and transverse diameters, and on other morphologic features in the cavity and outlet.

As always when any subject is more deeply explored, it turns out to be not as simple as at first appeared. Caldwell and Moloy soon found that pelvis were not always of pure type but that mixed forms exist, one part of the pelvic brim or cavity or outlet conforming to one type and another part to another type. So we have the gynecoid-android, the gynecoid-anthropoid, the gynecoid-flat, etc. Dr. Steele in his own studies has followed the classification of Caldwell and Moloy, and in this connection has endeavored to simplify it and to devise means for the easier clinical recognition of the various pure and mixed types. As every obstetrician has not access to the precision stereoscope, and even if he had may not be trained in its use, he has sought for simple clinical methods of diagnosis.

In this connection Dr. Steele has brought out several very interesting points:

1. That clinical measurement of the anteroposterior diameter of the brim will reveal only one-half of the truly contracted pelvis. This seems to be an argument for the more extended use of roentgenologic pelvimetry. When there is a shortened anteroposterior of the brim he has established the fact that the pelvis is more likely to be of the android or platypelloid type than the anthropoid or gynecoid.

2. That a diminution in the transverse of Michaelis' rhomboid is frequently an indication of an android pelvis. This measurement he calls the posterior transverse. This to me was very interesting, for in Scotland we, as students, always had emphasized to us the importance of Michaelis' rhomboid. Any diminution of its transverse diameter was regarded as an indication of a rachitic flat pelvis, of which, as you know, we had a great many there in those days. But probably many of the pelvis we classed as rachitic were really android. Dr. Steele, I am sure, will not take it amiss if I thus hint that his posterior-transverse diameter is nothing new. His interpretation of its variations, however, is new.

Dr. Steele has also stressed the importance of the anterior transverse diameter in relation to the capacity of the forepelvis. A short anterior transverse may entirely nullify a long anteroposterior in an anthropoid pelvis and make delivery impossible.

I feel that it will only be after many more studies of the painstaking character of the work just presented to us that we shall arrive at a simple working classifica-

5. All forms encountered must be provided for in a formal classification. The terminology of Caldwell and Moloy has been employed because it provides for the recognition of pure and mixed types. The terms have correct etymology. Care must be utilized when combining their nomen-

TABLE VII. PERCENTAGE INCIDENCE OF NORMAL\* AND CONTRACTED† PELVES ACCORDING TO MORPHOLOGY IN 1,000 CASES

| MORPHOLOGY   | NORMAL |          | CONTRACTED |          | TOTAL  |          |
|--------------|--------|----------|------------|----------|--------|----------|
|              | NUMBER | PER CENT | NUMBER     | PER CENT | NUMBER | PER CENT |
| Gynecoid     | 409    | 72.6     | 154        | 27.4     | 563    | 56.3     |
| Android      | 107    | 54.5     | 89         | 45.5     | 196    | 19.6     |
| Anthropoid   | 158    | 92.9     | 12         | 7.1      | 170    | 17.0     |
| Platypelloid | 26     | 36.6     | 45         | 63.4     | 71     | 7.1      |
| Total        | 700    | 70.0     | 300        | 30.0     | 1,000  | 100.0    |

\*CO. = 10.5 cm. and over.

†CO. = under 10.5 cm.

clature with that of Thoms. While the terms "dolichopellic" and "anthropoid," "platypellic," and "platypelloid" are interchangeable, there is still some question regarding the admissibility of doing so with the "brachypellic" and "gynecoid," and the "mesatipellic" and "android" types.

6. The problem presented by the irreducible multiplicity of form can be lessened by individual classification of the anterior and posterior segments of the inlet.

7. The combined isometric and stereoscopic technique provides an excellent opportunity for the determination of size and for the study of morphology of the obstetric pelvis.

8. Clinical pelvimetry, using revised concepts, has shown considerable promise and is being investigated further. In this, the posterior transverse diameter should prove of assistance in detecting the android posterior segment.

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In the second place, the authors of the Caldwell-Moloy classification seem to consider the transversely oval pelvis as the typical feminine pelvis and have labeled it gynecoid. Actually, there is no reason to believe that a transversely oval pelvis is more characteristically feminine than is a circular pelvis, or a pelvis with a slight increase of anteroposterior diameters over the transverse. To label it as such is rather falsely to assume that the individual is more feminine in her sexuality than is the individual with the round or oval pelvis anteroposteriorly, and to assume further that trends in development of the human female pelvis is in this direction.

If pelvises must be classified from the general point of view of anthropology, would it not be better to limit this classification to the contour of the pelvic inlet? In this connection, I would subscribe to the classification proposed by Thoms of dolichopellic, mesatipellic and brachypellic, referring, respectively, to the anteroposterior oval, the round pelvis, and the transverse oval inlet. A second main grouping of pelvises should bear upon the general size of the pelvis, namely: justo minor, or generally contracted; average; and justo major. Finally, a third grouping of pelvises should give consideration to environmental factors. In this group there should be included the masculine type of pelvis, the pelvis affected by disease, rickets, osteomalacia, etc.; the pelvis affected by trauma; the pelvis affected by the congenital absence of one or more portions of the pelvis such as the Naegele or Robert pelvis, etc.

With these considerations in mind, a pelvis might be found "dolichopellic and average in size," or "generally contracted and rachitic" or "masculine in type and average in size," etc. With such terms, I think we might have something we could convey to our students.

In short, I dislike to give up the old classification based on environmental factors, and I really see no reason why one of them, the masculine type of pelvis, should be taken from this group and placed in a special classification otherwise based on anthropologic considerations. I know of no reason for calling the transversely oval pelvis feminine to the exclusion of other equally feminine types. If pelvises are to be studied anthropologically, we must exercise some discrimination in our endeavor to establish a clinical classification on such criteria.

DR. STEELE (closing).—In reply to Dr. Montgomery, I would say that we are talking about morphology more than anthropology. It is the shape of the pelvis that is of interest in evaluating it from an obstetric standpoint.

The inclusion of the so-called sexual characteristics is incidental to the morphology. The android or the male form is important, for in all studies it has been found to be associated with more trouble than any other type of pelvis.

When classification is referred to provision is made for a description of the canal and the outlet. It should be remembered, however, that any kind of canal or outlet may be associated with any kind of inlet and for that reason we must have a very flexible system of classification. The great number of forms is, I think, justified since 50 per cent of the material examined was made up of mixed forms. Any change in either the anterior or the posterior segment of the pelvis alters its obstetric value.

Now as to the use of the so-called etiologic and pathologic forms in classification, I have to date examined about 1,600 pelvises and I have yet to encounter one which we could not classify on its morphologic basis alone.

tion of pelvic types. I do not believe we should worry too much about actual classification now. The important thing is to study each individual case with all the means at our disposal. With an accumulation of such cases we shall ultimately be able to form a better prognosis of labor, using clinical measurement, roentgenologic pelvimetry, and stereoscopic visualization as our guides.

When that classification is possible I feel that more than brim measurements and shape will have to be taken into account. Classification is not an end in itself. It is of value only as a sort of ready reckoner to enable us to arrive easily at an assessment of pelvic shape and size, which in its turn has its practical application in enabling us to form a prognosis of labor and to apply the proper maneuvers at the proper time when difficulty arises.

DR. THADDEUS L. MONTGOMERY, PHILADELPHIA, PA.—My own interest in this subject has to do with the employment of the method in teaching. Through the past years I have had some difficulty in making this method clear and I have turned over in my mind a number of times why such should be the case. I am inclined to believe that the principal difficulty is due to the confusion that has been created by combining the sexual influences with the anthropologic. Why is it more essential to include the masculinizing influence in a morphologic classification than it is to include, for example, the various factors of disease?

Evidently the evolution of the human pelvis is from the anthropoid or dolichopelvic type of inlet through the round pelvis and toward the transversal oval pelvis, as is set forth in Thoms' classification. Why should we call a transversely oval pelvis a gynecoid pelvis, indicating that it is the true female pelvis? The round one may be just as typically feminine as the transversely oval. Furthermore, there is now an effort to include an android pelvis.

I think it would simplify our classification then if we would place the anthropologic considerations second to factors of individual heredity such as the large pelvis, the narrow and the small pelvis. In a third column could be placed the environmental factors, including the masculinizing influences, the endocrine effects, the factors of disease and of trauma, and all of those factors which make for an irregular pelvis.

We do not routinely employ such methods of mensuration as described by Dr. Steele for the accurate determination of pelvic dimensions at the Temple University Hospital. Instead, we resort to the anteroposterior and lateral film of the pelvis at term or during labor to determine in what fashion the presenting part is adapting itself to the pelvic inlet, believing that on the basis of such films and the clinical examination, we are able to formulate the methods of management in frank or relative disproportion.

The rather wide acceptance of the Caldwell-Moloy classification of the pelvis throughout the country has, however, made it necessary in most medical schools to present it as at least one method of pelvic study. Nevertheless I have personally had considerable difficulty in presenting this classification to medical students and internes in such fashion that it will fulfill practical requirements as well as amplify the knowledge of pelvic anatomy. The difficulties are as follows:

First, the inclusion of so-called android types of pelvis and a complicating factor to what otherwise might be considered an anthropologic classification. To most of us the android pelvis means a masculine type of pelvis of funnel shape, with some peculiarities of inlet contour and unusual ruggedness of structure. It is generally associated with the less feminine type of individual, with irregular menstruation, infertility, and difficult labors. Actually, it represents a type of pelvis which has been subjected to environmental factors, namely, disturbance in the internal secretion and constitution of the individual. There seems hardly any more reason to include it in the so-called primary grouping than to include perhaps the rachitic pelvis or an osteomalacic pelvis.

tention is confined principally to two features, namely: The evolution of the shape of the female pelvic inlet and the development of the sexual differences in bony pelvis.

Most of our previous knowledge of pelvic development has been based upon the direct examination of fetal and adult pelvises, and a few studies of children's pelvises, based upon external measurements in living subjects. The majority of these studies were made during the latter part of the last century. So far as I am aware, roentgenometric examination has not previously been used for this purpose. The first real milestone in our knowledge of pelvic development was made by Litzmann,<sup>5</sup> who, in 1861, established the mechanical theory of pelvic development. He contended that trunk weight was one of the main factors in the formation of the final pelvic shape. On the assumption that the inlet of the fetal pelvis was longer than broad and that the inlet of the adult female pelvis was broader than long, Litzmann built up the idea that this change in shape was brought about through the sinking forward of the sacral promontory due to the increasing influence of trunk weight as the upright position was assumed. Shortly afterward Duncan<sup>6</sup> agreed with the fundamental changes in shape but gave a different explanation of the mechanics involved. On the other hand, Kehrer<sup>7</sup> believed that muscular tension or pull in extrauterine life was the principal factor in the development of the pelvic shape. In 1876 Fehling<sup>8</sup> published a detailed study of 130 fetal pelvises in which he concluded that the shape of the pelvis was determined by certain inherent properties or growth potentials, which were but little influenced by extraneous factors. He showed conclusively for the first time that the fetal pelvic inlet was broader than long and argued that trunk weight had little influence on the shape of the pelvis. As a corollary to his conception he believed that male and female pelvises could be distinguished even as early as the fourth month of fetal life. In 1899, Thompson<sup>9</sup> studied 8 fetal pelvises and came to similar conclusions with regard to the sex differences. In 1894 Konikow<sup>10</sup> measured the pelvises (external measurements) of 120 individuals ranging in age from birth to 20 years and came to opposite conclusions. He could discover no differences between the two sexes until after puberty. Williams<sup>11</sup> was inclined to agree with Fehling, though he never investigated the subject specifically. Recently Yamamura<sup>12</sup> reported a careful study of 140 fetal pelvises, one-half of which were male and one-half female. This author was the first to apply statistical analysis to his figures. He was unable to find significant differences between male and female pelvises, except for a slightly smaller posterior segment at the inlet and a slightly greater tendency to narrow toward the outlet in the males, though he seems to have accepted Fehling's idea that sex differences exist at an early period of fetal life. While many other authors have contributed to our knowledge of pelvic development, the broad outlines of the principal theories and facts are included above.

## OBSERVATIONS OF THE DEVELOPMENT OF PELVIC CONFORMATION\*

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Hospital)*

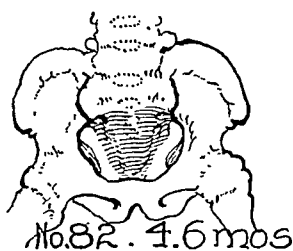
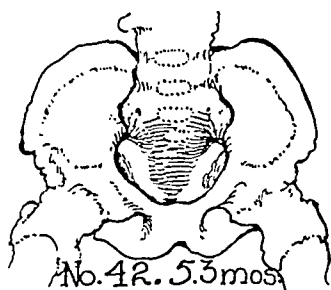
**D**URING the last fifteen years considerable advance has been made in our knowledge of the human bony pelvis through the use of roentgenologic examination. Many workers have contributed to the newer knowledge. The well-known studies of Thoms<sup>1, 2</sup> and of Caldwell and Moloy<sup>3, 4</sup> deserve special mention. The most fundamental of the new conceptions which we have gained is that the adult pelves of both males and females vary considerably in final shape without relation to specific causative diseases. We now know, for example, that the inlet of the adult female pelvis may be broader than long, equally as broad as long, or longer than broad. While variations of this character have long been recognized, they have been correlated principally with race, or degree of civilization. It has been said by anthropologists that women of the more primitive races possessed pelves of the long oval type, like those of the great apes, while women of the more civilized peoples had pelves of the platypelloid shape. It took the roentgenologic studies of the last decade to reveal that considerable proportions of dolichopellic, mesatipellic, and platypellic pelves existed in our contemporary population. The obstetric significance of these variations has received much attention and clarification, but as yet very little work has been directed toward tracing the development of such variations, either in regard to the time of occurrence or to the etiology. Such questions as the following remain to be answered: Are the variations in shape which are present in adult women observable in young girls? Are such variations observable in the fetal period? In short, are individuals endowed with factors which make for a given pelvic shape, which they thereafter retain unless influenced by specific diseases, such as rickets, or do all individuals start out life with pelves which are essentially similar which only later become modified in form? If the latter supposition is true, what are the changes, when do they occur, and what brings them about? When do the sexual differences appear and what brings them about? It is with these phases of the subject that the present investigation concerns itself. In this report at-

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justifiable, even when treated statistically, unless the number of cases is extremely large. This applies to the figures of Fehling and of Yamamura as well as to my own\*

## MALE



## FEMALE

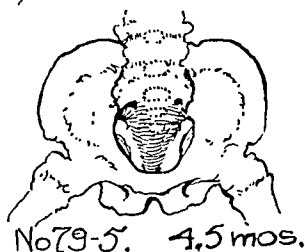
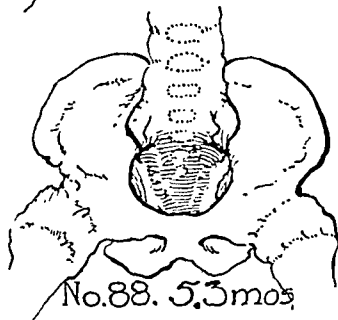
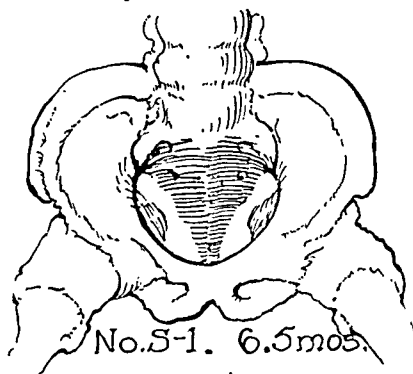


Fig. 2.

Figs. 2 and 3.—Comparison of the pelvic inlet in fetal male and female pelvis of different ages.

In all of the fetal pelvises, male as well as female, the pelvic inlet was found to be similar and characteristic. In all instances the outline of the inlet was smooth, though rather squared off anteriorly. The shape of the

\*Scale drawings of the fetal male and female pelvises of comparable ages were made by Mr. Ralph Sweet and are reproduced in Figs. 2 and 3. They give a much better idea of the various characteristics than do the actual measurements.

The material upon which the present observations are based consisted of 27 fetal pelvises, 10 female and 17 male, varying in age from three and one-half to ten months, which were studied and measured directly, and the roentgenometric examination of the pelvises of 98 girls and 45 boys, varying in age from three to eighteen years. Some observations upon a portion of the latter material, including the method of roentgenometric examination, have been reported previously by Morton and Hayden.<sup>13</sup> The fetal pelvises for the most part were from the collection of beautifully prepared fetal skeletons in the Department of Anatomy at the University of California. They were prepared and mounted by Mr. Rudolph Skarda.<sup>14</sup> This material was made available

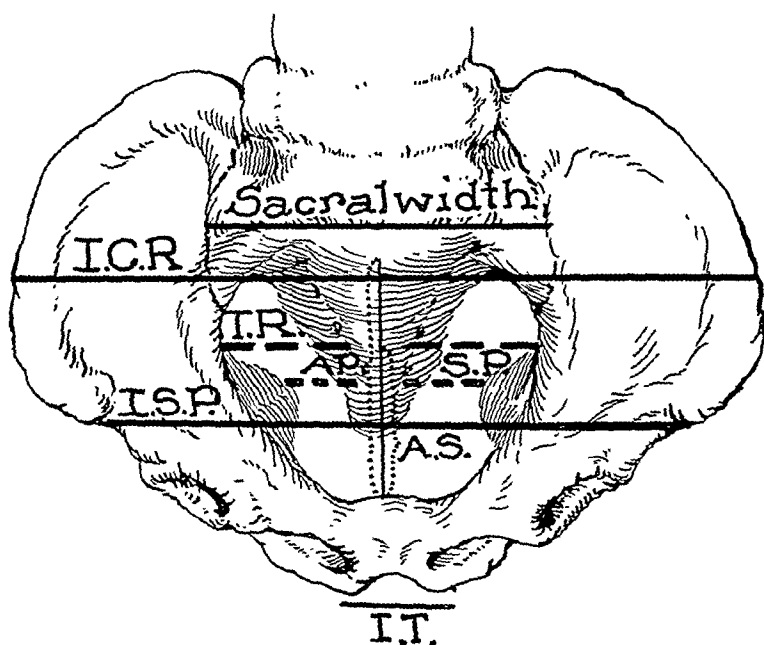


Fig. 1.—Diameters measured. Indices calculated (1) pelvic  $\frac{AP \times 100}{TR}$ ; (2) sacral  $\frac{sacroal\ width \times 100}{ICR}$ ; (3) post. space  $\frac{AP}{AS}$ .

to me by Prof. John Saunders, who has given me invaluable assistance in this study. The pelvises were considered from the point of view of the size and shape of the inlet, the sacrum, the sacrosciatic notch, the pubic arch, and the pelvic outlet. Various diameters were measured and certain pertinent indices calculated as indicated in Fig. 1 and recorded in Table I. The pelvises were examined in the wet state in order to avoid changes in shape due to drying, and each measurement was made three times, the mean being taken as the final figure. Differences in the methods of preservation, whether wet or dry, have given rise to much of the confusion in results in the past. However, experience in making the measurements, many of which were of very small order, has convinced me that absolute accuracy is impossible. I, therefore, believe that conclusions based upon differences of fractions of a millimeter are not

the fourth month of fetal life the sacrum was almost straight; from the fourth to the tenth month one could observe a definite curve, which did not change appreciably during this period. The first sacral vertebra occupied a higher position than it does in children and adults, so that the posterior extremity of the anteroposterior diameter of the inlet fell not at a promontory formed by the upper border of this vertebra but at the upper border or the middle of the second sacral vertebra. This means that the anteroposterior diameter of the pelvic inlet in the fetus is not directly comparable to that which is observed roentgenologically in the adult, in the sense that the posterior extremity of this diameter lies at a much lower point on the sacrum in the former case than it does in the latter. From the viewpoint of an "obstetric conjugate," they are comparable, for in this sense they are both measures of anteroposterior space at the inlet. Both Fehling and Yamamura made similar observations regarding the position of the sacral promontory. However, even if one employs the upper border of the first sacral vertebra as the posterior extremity, the anteroposterior diameter is still smaller than the greatest transverse measurement.

Except for general increase in all diameters, there were no marked changes in the shapes of the fetal pelvises from the youngest to those of term size. The drawings illustrate this well.

In agreement with Yamamura, I was unable to distinguish sexual differences, though the small number of pelvises does not permit unqualified conclusions. Both Fehling and Thompson believed that they could make sexual distinctions as early as the fourth month and the latter described for his fetal male pelvises the well-known characteristics of adult male pelvises, such as a narrowing toward the outlet, narrower interischial spines and tuberosities, and a narrower sacrosciatic notch. However, Thompson's conclusions were drawn from a comparison of four male with four female pelvises and may well be untrustworthy. In my material, both the sacrosciatic notches and the subpubic angles varied considerably in individual specimens. Neither was characteristically wide nor narrow in the respective sexes. There were no statistically significant sexual differences in the pelvic index, the sacral index, nor in the position of the greatest transverse diameter of the inlet (Table I). Yamamura's detailed observations support these findings, except for the last item mentioned. His figures indicated that in the male the greatest transverse diameter of the inlet lay closer to the sacrum than it did in the female.

I have no observations bearing upon the changes in the pelvis from birth to three years of age. Konikow's study indicated that there was a striking increase in both the transverse and the anteroposterior diameters of the pelvis in the first year of life but that the anteroposterior diameter increased at a much slower rate than did the transverse diameters in the following four years. This fact he attributed to the in-

inlet was that of a transverse ovoid, the greatest transverse diameter invariably exceeding the anteroposterior diameter. Casual inspection of the drawings gives one the impression that the inlet is longer than broad, whereas the reverse is true. The same thing obtained in examining the

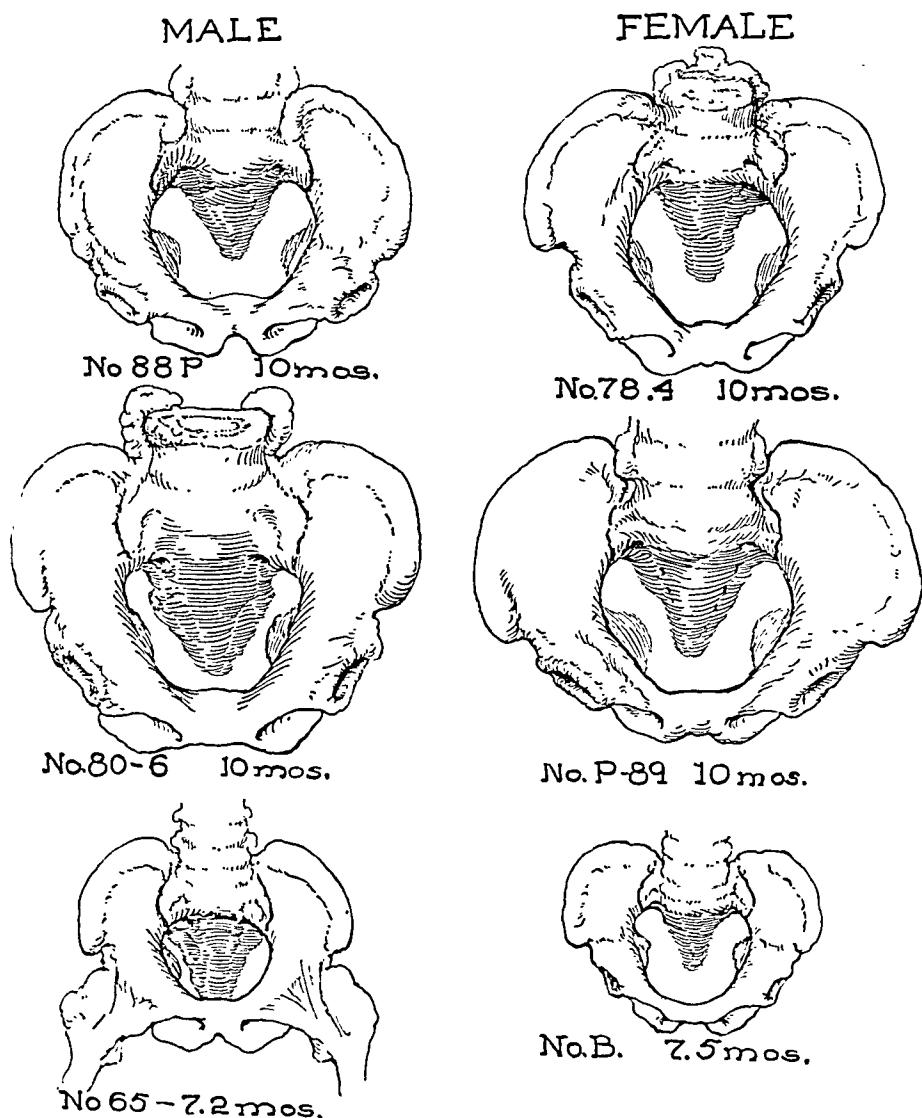


Fig. 3.

actual pelvis. Reference to Table I reveals that the pelvic index of Turner ( $\frac{\text{Anteroposterior diameter of inlet} \times 100}{\text{Greatest transverse diameter of inlet}}$ ) fell below 90 in all instances except two; in the two exceptions the indices were 91 and 96, respectively. These figures give mathematical expression to the broader than long shape of these pelvises.

The sacrum presented a rather straight flat surface, forming a more obtuse angle with the lumbar spine than one finds in later life. Before



TABLE II. THE DETAILS OF THE 27 CASES IN WHICH REPEAT EXAMINATIONS WERE MADE

| NUMBER | NAME        | AGE<br>YR. | PELVIC INLET           |                                  |                            | AP<br>AS | PELVIC<br>INDEX |
|--------|-------------|------------|------------------------|----------------------------------|----------------------------|----------|-----------------|
|        |             |            | TRANS-<br>VERSE<br>CM. | ANTERO-<br>POS-<br>TERIOR<br>CM. | ANTERIOR<br>SEGMENT<br>CM. |          | AP × 100        |
|        |             |            |                        |                                  |                            |          | TR              |
| 111311 | Clowdus     | 3          | 6.6                    | 6.8                              | 3.9                        | 1.743    | 103             |
| 146059 | Clowdus     | 6          | 7.4                    | 8.4                              | 5                          | 1.680    | 114             |
| 117661 | Hunt        | 3          | 7.6                    | 7.8                              | 4.3                        | 1.813    | 102             |
| 157022 | Hunt        | 7          | 8.6                    | 8.6                              | 5.5                        | 1.563    | 100             |
| 115291 | Roth        | 4          | 6.6                    | 6.2                              | 3.9                        | 1.589    | 94              |
| 155513 | Roth        | 7          | 7.7                    | 7.7                              | 5.1                        | 1.509    | 100             |
| 107193 | Latierzo    | 4          | 7.5                    | 7                                | 4.2                        | 1.666    | 93              |
| 154797 | Latierzo    | 8          | 8.5                    | 8.5                              | 5.1                        | 1.666    | 100             |
| 117304 | Holt        | 4          | 8                      | 8                                | 4.9                        | 1.550    | 100             |
| 154334 | Holt        | 8          | 8.3                    | 8.9                              | 5.8                        | 1.534    | 107             |
| 112259 | Filice      | 6          | 7.2                    | 7.1                              | 4.1                        | 1.710    | 99              |
| 157024 | Filice      | 10         | 7.4                    | 8                                | 4.8                        | 1.666    | 108             |
| 116965 | MacIntyre   | 7          | 8                      | 8.5                              | 4.1                        | 1.670    | 106             |
| 153404 | MacIntyre   | 10         | 8.7                    | 9.3                              | 6.5                        | 1.431    | 107             |
| 106428 | Piccini     | 8          | 8.9                    | 9                                | 5.9                        | 1.525    | 101             |
| 129814 | Piccini     | 10         | 9.5                    | 9.6                              | 6.5                        | 1.476    | 101             |
| 145315 | Piccini     | 12         | 10.3                   | 10                               | 6.5                        | 1.538    | 97              |
| 107316 | Smith       | 8          | 8.5                    | 10                               | 6.8                        | 1.470    | 117             |
| 152740 | Smith       | 12         | 10.3                   | 11                               | 7.3                        | 1.507    | 107             |
| 119016 | Taylor      | 8          | 7.2                    | 8                                | 5                          | 1.60     | 111             |
| 152690 | Taylor      | 11         | 7.9                    | 9                                | 5.9                        | 1.525    | 114             |
| 119210 | McLean      | 8          | 8.6                    | 10.5                             | 6.2                        | 1.69     | 122             |
| 145987 | McLean      | 10         | 9.9                    | 10.9                             | 6.5                        | 1.677    | 110             |
| 106224 | Dorado      | 9          | 8.6                    | 9.5                              | 6.5                        | 1.461    | 110             |
| 145989 | Dorado      | 13         | 11.3                   | 10.5                             | 7.1                        | 1.479    | 93              |
| 106782 | Sordello    | 10         | 9.6                    | 10.8                             | 7                          | 1.54     | 112             |
| 151980 | Sordello    | 13         | 13                     | 12.3                             | 7.7                        | 1.597    | 95              |
| 115759 | Morton      | 10         | 8.4                    | 9.8                              | 5.5                        | 1.78     | 116             |
| 129554 | Morton      | 11         | 9.6                    | 10.5                             | 5.8                        | 1.81     | 109             |
| 145314 | Morton      | 12         | 9.8                    | 10.2                             | 5.9                        | 1.729    | 104             |
| 118240 | Phillips    | 10         | 7.8                    | 10.1                             | -                          | -        | 129             |
| 152530 | Phillips    | 13         | 8.6                    | 10.4                             | 6.7                        | 1.552    | 121             |
| 116902 | Hantnee     | 11         | 8.5                    | 9.8                              | 6.7                        | 1.463    | 115             |
| 145973 | Hantnee     | 13         | 8.9                    | 10.5                             | 6.5                        | 1.615    | 118             |
| 109078 | Hofmann     | 11         | 9.5                    | 10                               | 6.5                        | 1.54     | 105             |
| 152224 | Hofmann     | 15         | 11.8                   | 10.12                            | 6.6                        | 1.545    | 86              |
| 106895 | Hengst      | 11         | 9.5                    | 11.5                             | 7                          | 1.57     | 121             |
| 151476 | Hengst      | 15         | 12                     | 12.6                             | 7                          | 1.80     | 105             |
| 110909 | Azevedo     | 11         | 8.8                    | 10.5                             | 6.1                        | 1.721    | 119             |
| 152864 | Azevedo     | 14         | 11.2                   | 12                               | 6.9                        | 1.739    | 107             |
| 110879 | Johnson     | 11         | 9                      | 10.6                             | 7.1                        | 1.492    | 117             |
| 129814 | Johnson     | 12         | 10.1                   | 11                               | 7.6                        | 1.447    | 109             |
| 145317 | Johnson     | 13         | 10.8                   | 11.4                             | 7.3                        | 1.561    | 106             |
| 156811 | Johnson     | 14         | 12.1                   | 12.2                             | 7.6                        | 1.601    | 101             |
| 108347 | Pina        | 11         | 9.5                    | 9.8                              | 6.3                        | 1.55     | 103             |
| 151226 | Pina        | 14         | 12.5                   | 11.2                             | 7                          | 1.60     | 90              |
| 106778 | Misenheimer | 11         | 11.4                   | 9.3                              | 6                          | 1.55     | 82              |
| 151766 | Misenheimer | 15         | 11.7                   | 10.1                             | 6.6                        | 1.53     | 87              |
| 105622 | Silverman   | 12         | 9                      | 11                               | 6.7                        | 1.641    | 122             |
| 131354 | Silverman   | 14         | 11                     | 11.4                             | 6.6                        | 1.727    | 104             |
| 145316 | Silverman   | 16         | 11.1                   | 12                               | 6.6                        | 1.818    | 108             |
| 106671 | Debekker    | 12         | 9.5                    | 10.2                             | 6.5                        | 1.569    | 107             |
| 152027 | Debekker    | 16         | 12.8                   | 11.4                             | 6.8                        | 1.676    | 89              |
| 116002 | Aceves      | 12         | 9.4                    | 10.5                             | 6.4                        | 1.646    | 111             |
| 151702 | Aceves      | 15         | 11.5                   | 11.5                             | 6.5                        | 1.769    | 100             |
| 117661 | Iannochona  | 12         | 11.3                   | 12.3                             | 6.2                        | 1.983    | 109             |
| 157028 | Iannochona  | 15         | 12                     | 13.2                             | 6.8                        | 1.919    | 110             |
| 111350 | Martin      | 13         | 11.2                   | 11.5                             | 6.6                        | 1.742    | 102             |
| 153117 | Martin      | 17         | 12                     | 11.7                             | 7.3                        | 1.602    | 98              |

TABLE I. MEASUREMENTS OF 27 FETAL Pelves IN MILLIMETERS. AGE BASED ON SITTING HEIGHT (STREETER), TOTAL LENGTH, AND MENSTRUAL HISTORY

| No.  | SEX | LUNAR MONTH AGE | PELVIC INLET |         |                  | ICR MM. | ISP MM. | SACRAL WIDTH MM. | ISCHIAL SPINES MM. | INTERTUBEROUS MM. | AP AS | SACRAL INDEX | PELVIC INDEX |
|------|-----|-----------------|--------------|---------|------------------|---------|---------|------------------|--------------------|-------------------|-------|--------------|--------------|
|      |     |                 | TRANS. MM.   | AP. MM. | ANT. SEGMENT MM. |         |         |                  |                    |                   |       |              |              |
| 81   | M   | 3.3             | 6.2          | 4.3     | 2.4              | 14.9    | 13.1    | 7                | 5.6                | 2.7               | 1.791 | 49           | 69           |
| 44   | M   | 3.5             | 7.3          | 7       | 5                | 18      | 16.1    | 8.8              | -                  | 4.2               | 1.400 | 44           | 96           |
| 64   | M   | 3.7             | 8.1          | 6       | 4                | 19      | 17      | 10               | 4.9                | 4                 | 1.500 | 53           | 74           |
| 50   | F   | 3.8             | 9.6          | 7       | 5                | 23      | 20.5    | 10               | 7                  | 5                 | 1.400 | 44           | 73           |
| 49   | F   | 4.0             | 9            | 7       | 5                | 22.9    | 21.2    | 10.4             | 6                  | 4.7               | 1.400 | 45           | 78           |
| 86   | M   | 4.1             | 9            | 7       | 5.1              | 20.8    | 19      | 10.1             | 5.9                | 5.5               | 1.372 | 48           | 78           |
| 84   | M   | 4.2             | 9.9          | 7       | 5.8              | 24.1    | 23      | 11               | 5.5                | 4.4               | 1.207 | 46           | 71           |
| 43   | F   | 4.5             | 11.2         | 9.9     | 6.9              | 27.7    | 26      | 14               | 8.1                | 6.2               | 1.434 | 51           | 88           |
| 79-5 | F   | 4.5             | 13           | 10      | 6.5              | 32.2    | 29.1    | 13.4             | 8.5                | 6.2               | 1.538 | 42           | 77           |
| 82   | M   | 4.6             | 13           | 10.3    | 7                | 31.3    | 29      | 14               | 9.7                | 7                 | 1.471 | 45           | 79           |
| 8    | M   | 4.8             | 12.9         | 10.7    | 8.1              | 33      | 30.1    | 14               | 9.9                | 6.7               | 1.320 | 42           | 83           |
| 85   | M   | 5               | 13.2         | 11      | 8                | 33.5    | 29.8    | 15.9             | 8.5                | 6.4               | 1.375 | 48           | 83           |
| 88   | F   | 5.3             | 15.2         | 12.2    | 9.2              | 40      | 37.2    | 17               | 11.4               | 9.2               | 1.326 | 43           | 80           |
| 42   | M   | 5.3             | 15           | 12.1    | 8.6              | 38      | 34.5    | 17.2             | 9.4                | 8.1               | 1.406 | 45           | 81           |
| 77-3 | M   | 5.5             | 16           | 13      | 9                | 40      | 37.6    | 16.2             | 10.5               | 10.6              | 1.444 | 41           | 81           |
| 76-2 | M   | 5.5             | 16.2         | 12      | 7.7              | 38      | 36.3    | 17.4             | 10.2               | 10.6              | 1.558 | 46           | 74           |
| 45   | M   | 6.2             | 18           | 14.7    | 10.4             | 45      | 42      | 20               | 12.7               | 9.2               | 1.413 | 44           | 82           |
| 8-1  | F   | 6.5             | 20.2         | 17.1    | 11.9             | 48      | 44.7    | 22.6             | 13.8               | 10.8              | 1.437 | 47           | 85           |
| 65   | M   | 7.2             | 22.7         | 18      | 12.7             | 53.1    | 50      | 24               | 16                 | 11.9              | 1.417 | 45           | 79           |
| 8    | F   | 7.5             | 22.3         | 16      | -                | 48.2    | 44      | 24               | 18                 | 17.4              | -     | 49           | 72           |
| 80   | M   | 8               | 24.6         | 20.5    | 14               | 57      | 55.1    | 26.2             | 17.9               | 17.1              | 1.464 | 46           | 83           |
| Mt.  | M   | 8               | 23.6         | 21.4    | 13.8             | 53.2    | 51      | 24               | 17                 | 17                | 1.550 | 45           | 91           |
| P-90 | F   | 10              | 34.5         | 23.1    | 16.6             | 71.7    | 65.5    | 32.6             | 22.3               | 21.3              | 1.391 | 45           | 67           |
| P-89 | F   | 10              | 36           | 27.5    | 17               | 82      | 78.1    | 33.8             | 26                 | 24.3              | 1.617 | 41           | 76           |
| 80-6 | M   | 10              | 35.5         | 31.7    | 21               | 77.9    | 72.2    | 39               | 31.9               | 20.9              | 1.509 | 50           | 88           |
| 78-4 | F   | 10              | 30.6         | 27.4    | 18.2             | 70      | 67.7    | 32.8             | 28                 | 26                | 1.505 | 47           | 90           |
| P-88 | M   | 10              | 31.6         | 25      | 16.8             | 68.9    | 63.1    | 35.4             | 23.6               | 22.6              | 1.488 | 51           | 79           |

Pelvic Index  $\left( \frac{AP \times 100}{TR} \right)$  - Mean for { Females - 78.6 } Males - 80.6 Standard error of Difference = 1.054 .. not significant

Sacral Index  $\left( \frac{SW \times 100}{ICR} \right)$  - Mean for { Females - 45.4 } Males - 46.3 Standard error of Difference = 1.31 .. not significant

Posterior Space  $\left( \frac{AP}{AS} \right)$  - Mean for { Females - 1.449 } Males - 1.484 Standard error of Difference = 0.075 .. not significant

the femora tends to retard the increase in the anteroposterior diameter of the inlet, while the sinking forward of the sacral promontory results in an approximation of the posterior-superior spines of the ilia and thus a relative increase in the transverse measurements. Whether the

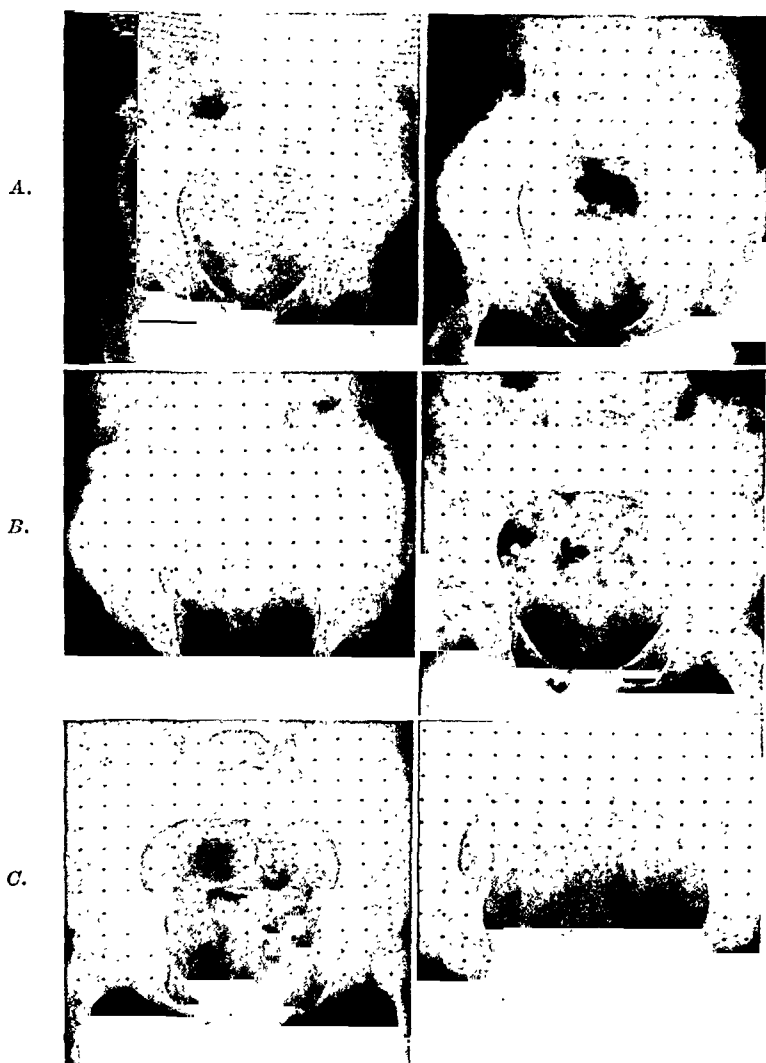


Fig. 6.—*A*, Girl, N. R. (No. H-115291 and H-155513). *B*, Girl, D. L. (No. H-107193 and H-154797). *C*, Girl, E. D. (No. H-106224 and H-145989). Two studies in each of three girls at different ages. *A* and *B* illustrate tendency to anteroposterior elongation of the pelvic inlet after approximate aged 6 years. *C* illustrates smoothing of the outline of the pelvic inlet and tendency to flattening as the child matures.

downward and forward movement of the promontory is due to trunk weight or to changes incident to a set pattern of bone growth as *Fehling* believed can only be speculated. The fact is that the movement occurs. The changes in position are well illustrated in Fig. 4.

The observations made in our previous roentgenometric study of children's pelves have been further documented. It was observed that until the age of puberty (11 years), there was little difference in the pelves

fluence of trunk weight. With Litzmann, he believed that as the child begins to walk the weight of the trunk is thrown anterior to the sacral promontory, which, therefore, sinks downward and forward as the sacrum rotates about a transverse axis in the region of the third sacral vertebra. The combination of this factor with the upward thrust of

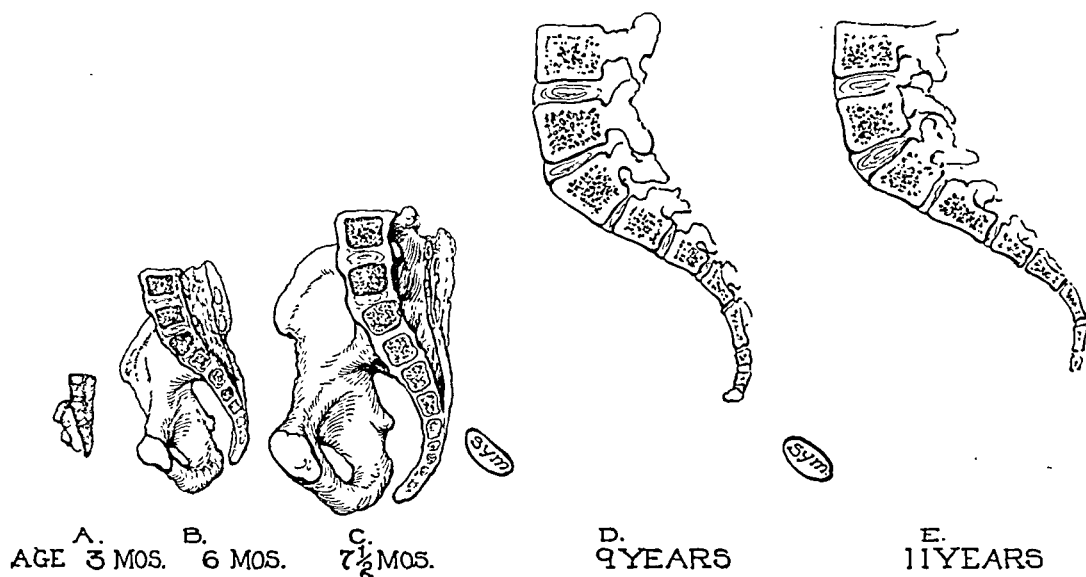


Fig. 4.—Illustrating the greater curvature imparted to the sacrum by the downward and forward movement of the promontory after the assumption of the upright position and walking.

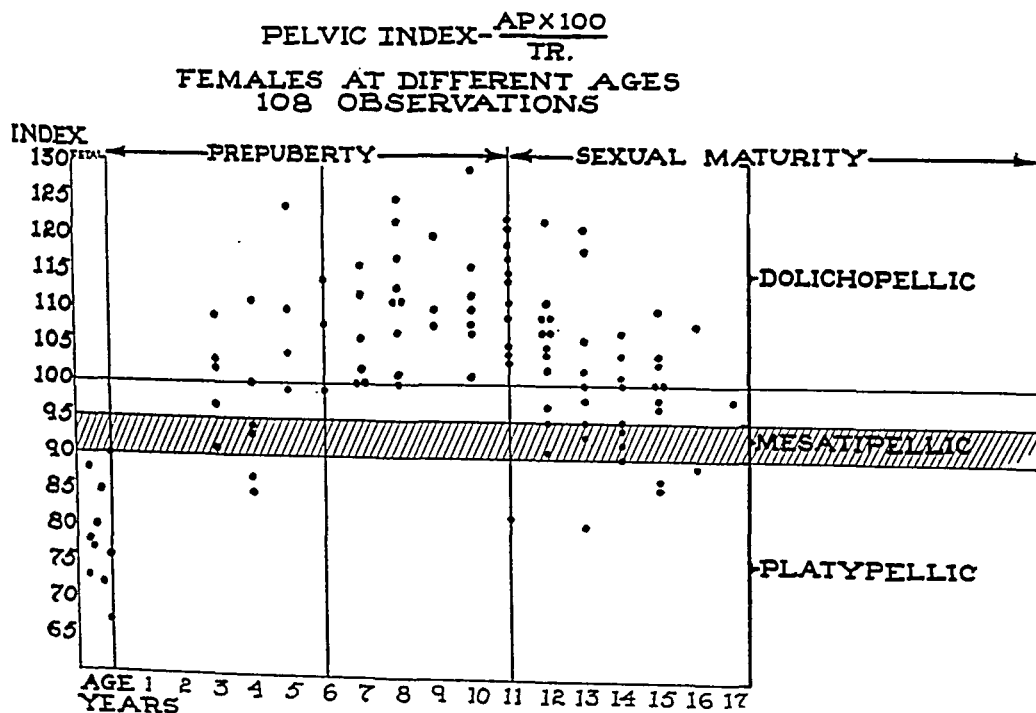


Fig. 5.—Illustrating the shift in the shape of the pelvic inlet at different ages.

acetabula, presumably due to the upward thrust of the femora. This was true in all of the children under eleven and invariably disappeared as maturity was reached.

In order to determine whether changes actually occurred in individuals as the above observations would seem to indicate, repeat studies

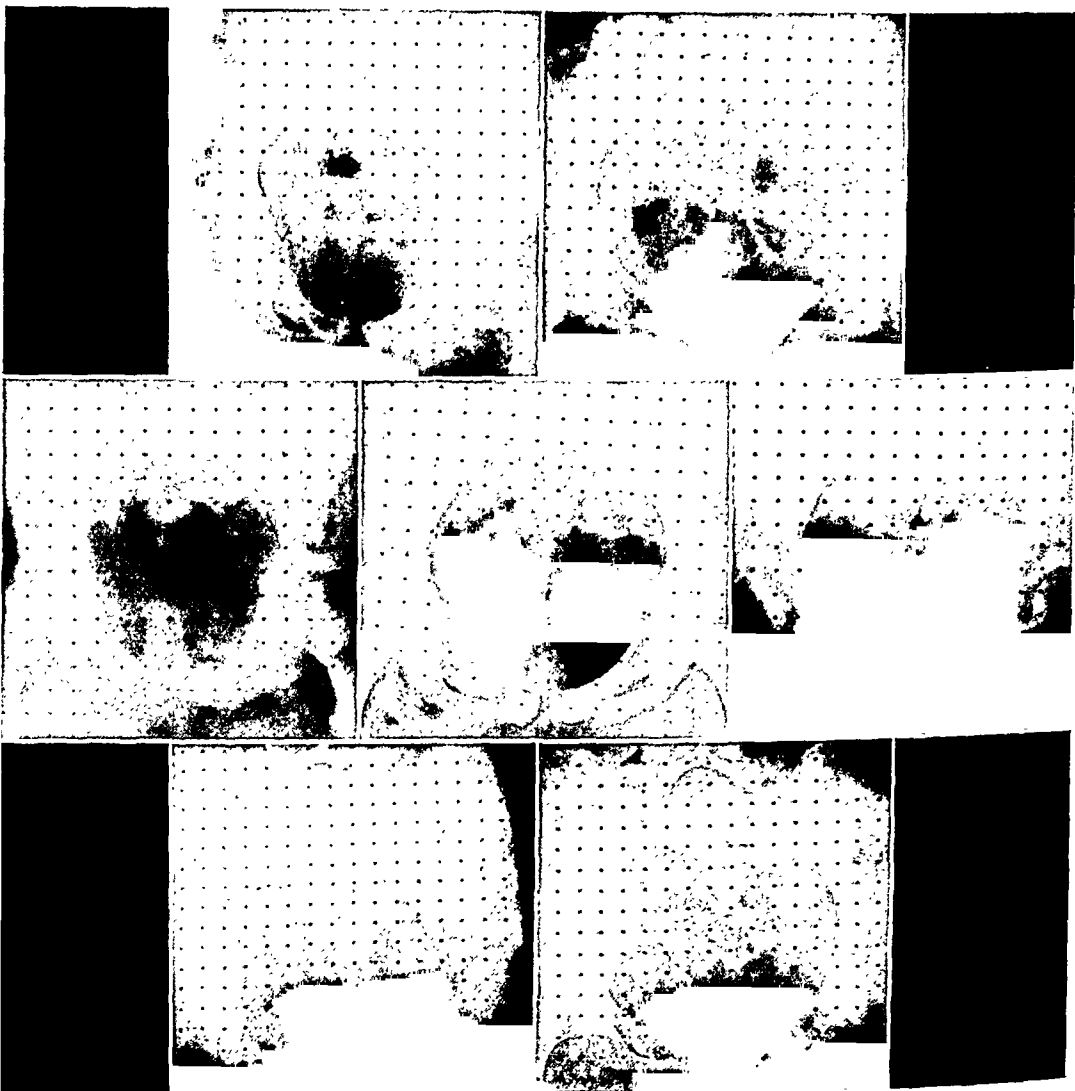


Fig. 8.—A, Girl, E. D. (No. H-106671 and H-152027). B, Girl, L. M. (No. H-115759, H-129554, and H-145314). C, Girl, I. M. (No. H-106778 and H-151766). A, Studies of the pelvic inlet in the same individual aged 12 years and 16 years, illustrating the smoothing of the outline of the pelvic inlet and the tendency to flattening as the child matures. B, similar studies in another individual showing retention of the anthropoid shape. C illustrates adult gynecoid shape at aged 11 years (possibly due to early puberty), with no further change in the shape four years later, though the size has increased.

were obtained in 27 of the cases. As expected, actual changes were observed (Figs. 6 to 8).

When repeat films were obtained in children originally studied at ages three, four, or five years, it was found that the inlet had changed in the three- or four-year interval from a round or broader than long

of boys and girls. The pelves of children three, four, and five years of age showed an inlet which was either round or broader than long in most instances. From age six years through age eleven years the pelves presented oval inlets, with the greatest diameter being the antero-posterior one. After eleven years, increasing proportions of the pelves

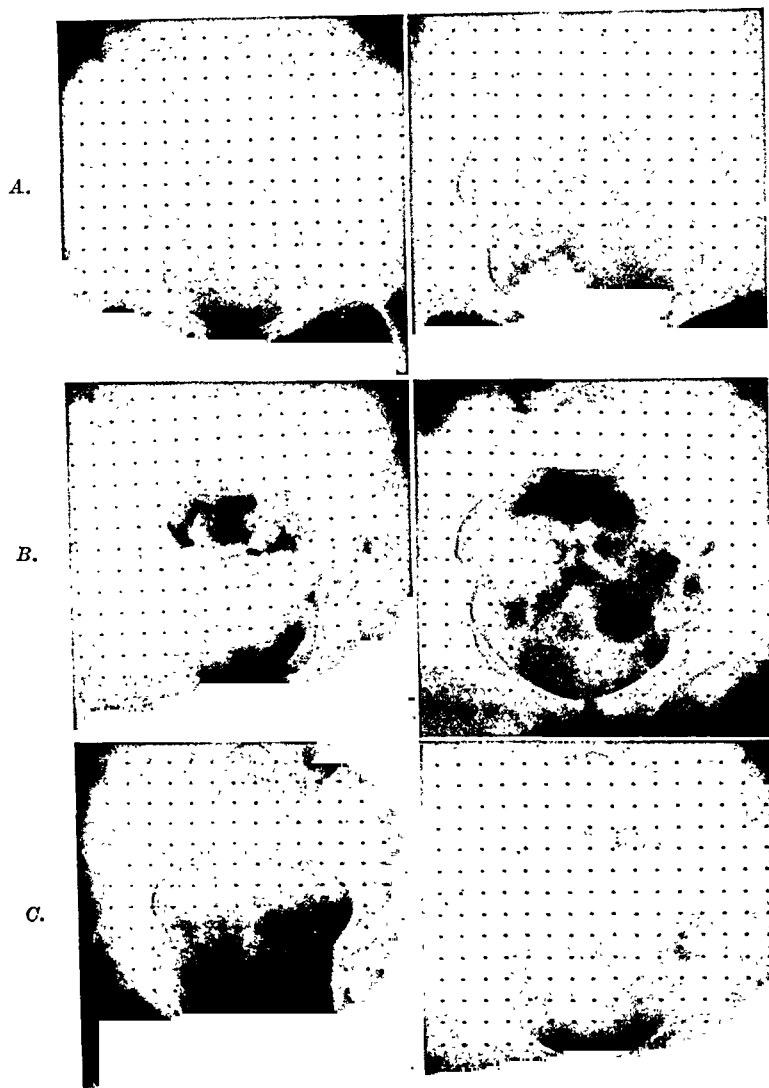


Fig. 7.—A, Girl, I. P. (No. H-108347 and H-151226). B, Girl, N. H. (No. H-106895 and H-151476). C, Girl, J. A. (No. H-116002 and H-151702). Additional serial studies in each of three girls. All illustrate the smoothing of the outline of the pelvic inlet and tendency to flattening as the child matures.

of the girls showed inlets which were again broader than long. The graph of pelvic indices (Fig. 5) illustrates these shifts in inlet shape graphically. All figures above 100 indicate inlets which were longer than broad. One other fact of interest was that in all of the children eleven years of age or younger, the inlet of the pelvis did not present a smooth outline but showed an inward bowing in the regions of the

tion, or variations in responsiveness to the sex hormone, or variations in the quantity of the hormone itself may be responsible.

The roentgenologic studies revealed no striking sexual differences before the age of puberty (eleven years was taken arbitrarily as the



Fig. 10.—Comparison of the pelves of boys and girls of the same prepuberty ages. Note the marked similarity in all views. A, Girl, aged 5 years. B, Boy, aged 5 years. C, Girl, aged 7 years. D, Boy, aged 7 years.

dividing line, with the full realization of individual variations from such an age), with two possible exceptions, as follows: (1) The position of the greatest transverse diameter of the inlet was slightly closer to the

shape to a longer than broad, or dolichopellic shape. When pelves, originally studied between the ages of six and twelve years, were re-studied at fourteen or fifteen years it was found that the inlet had lost its inward bowing in the acetabular regions and, in most instances, the inlet showed some degree of flattening again. The details of these repeat studies are given in Table II and are graphically illustrated in Fig. 9. While it seems likely that Fehling's idea of predetermined or inherited growth potentials as the main determinant in pelvic development is fundamentally sound, Konikow's observations and the facts presented point to other determinants as well. The assumption of the upright position, with the consequent upward thrust of the

### CHANGES IN PELVIC INDEX WITH CHANGES IN AGE

27 INDIVIDUALS —  $P.I. = AP \times 100 / TR.$

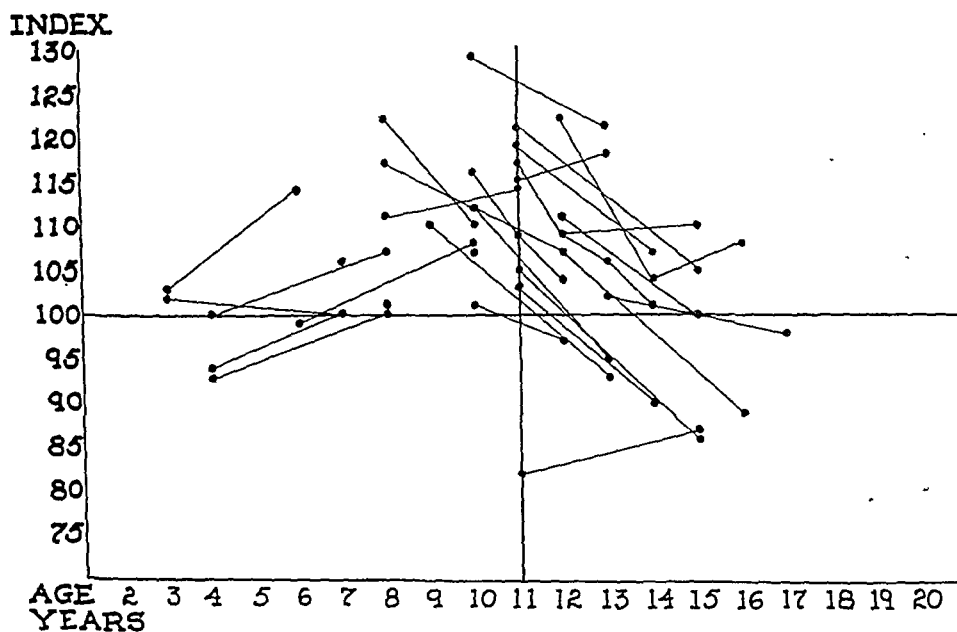


Fig. 9.—Illustrating the shift in the shape of the pelvic inlet at different ages in individuals.

femora seems to have a definite effect upon the shape of the pelvis, at least, it produces an inward bowing of the pelvic outline. What causes the change in the shape of the pelvis from platypelloid or round to dolichopellic in the years six to twelve can only be guessed. More violent running and walking while ossification is still incomplete, or sitting on school benches for long hours, or some entirely unknown factor may be responsible. In any event, the uniformity of this finding is striking. The tendency to flattening again after puberty most logically can be coupled with the appearance of the sex hormones. The reason for the retention of the dolichopellic shape by some individuals, and the assumption of varying degrees of flattening by others, is not clear. Nutri-



TABLE III. COMPARISON OF CERTAIN INDICES AND MEASUREMENTS IN BOYS AND GIRLS OF PREPUBERTY AGE. IN ONLY ONE RESPECT IS THERE A STATISTICALLY SIGNIFICANT DIFFERENCE. THE POSTERIOR SEGMENT OF THE INLET IS SMALLER IN THE MALE

| INDEX OR MEASUREMENT           | GIRLS 11 YEARS OF AGE AND LESS |       |                    | BOYS 11 YEARS OF AGE AND LESS |       |                    | COMMENT        |                              |      |             |
|--------------------------------|--------------------------------|-------|--------------------|-------------------------------|-------|--------------------|----------------|------------------------------|------|-------------|
|                                | NUMBER OF OBSERVATIONS         | MEAN  | STANDARD DEVIATION | NUMBER OF OBSERVATIONS        | MEAN  | STANDARD DEVIATION | THE DIFFERENCE | STANDARD ERROR OF DIFFERENCE |      | SIGNIFICANT |
| AP*                            | 53                             | 1.605 | 0.0774             | 34                            | 1.549 | 0.0953             | 0.056          | 0.0194                       | 2.8  | Probably    |
| AS                             | 56                             | 107.4 | 17.94              | 34                            | 107.5 | 9.69               | 0.1            | 3.34                         | 0.29 | No          |
| AP $\times$ 100<br>TR          |                                |       |                    |                               |       |                    |                |                              |      |             |
| S3<br>Related to AP as 10 cm.  | 49                             | 10.48 | 0.71               | 32                            | 10.72 | 0.642              | 0.24           | 0.1519                       | 1.5  | No          |
| S5<br>Related to AP as 10 cm.  | 49                             | 10.24 | 1.05               | 32                            | 10.21 | 0.753              | 0.03           | 0.2056                       | 0.1  | No          |
| SSN<br>Related to AP as 10 cm. | 46                             | 3.86  | 0.46               | 28                            | 3.71  | 0.469              | 0.15           | 0.112                        | 1.3  | No          |

\*AP represents the anteroposterior diameter of the inlet. AS represents that portion of the anteroposterior diameter which is anterior to the greatest transverse diameter. The smaller this quotient the closer is the greatest transverse diameter to the sacrum.

sacrum in the boys than it was in the girls (see  $\frac{AP}{AS}$  in Table III), and (2) the downward curve of the sacrum differed in the two sexes, while actual measurement of the distance from the symphysis to the middle of the third sacral vertebra (*S3*) and to the inferior border of the fifth sacral vertebra (*S5*), and measurement of the sacrosciatic notch (*SSN*) revealed no significant differences between means, and while the notches failed to differ in general appearance, the male sacrum took a rather abrupt downward swing just above its midpoint, whereas the female sacrum did not (Table III).

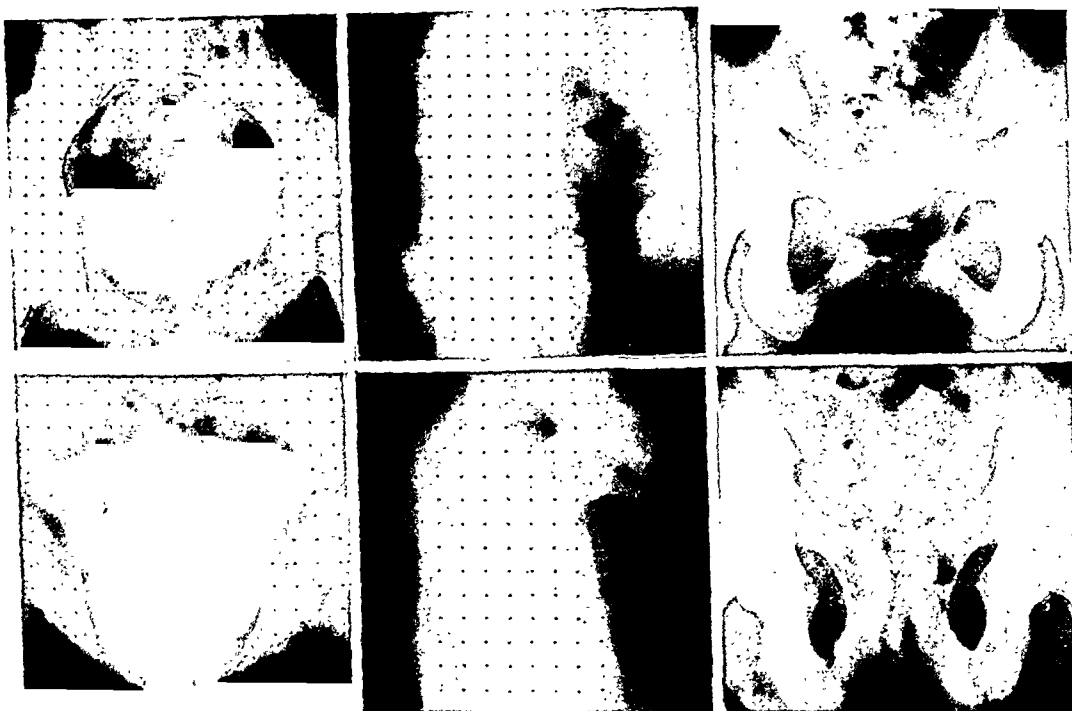


Fig. 11.—After puberty marked sexual differences appear. A, Girl, aged 15 years. B, Boy, aged 17 years.

After eleven years of age the well-known characteristics of adult female and male pelvis began to crop up and became increasingly apparent as the children were older (Figs. 10 and 11).

From the evidence at hand, it appears that only minor differences, possibly entirely insignificant, exist between the bony pelvis of males and females before puberty. At this time the pelvis of each sex take on definite characteristics which differ materially. It is felt that this is probably associated with the great increase in the sex hormones which is known to occur at this time, causing the marked genital and secondary sexual development so characteristic of this period.

More concrete substantiation of the idea that pelvic shape can be influenced by sex hormones is offered by the animal experiments of Hisaw,<sup>15</sup> in 1925, and Gardner,<sup>16</sup> in 1936. The former, working with the

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## DISCUSSION

DR. WILLIAM E. CALDWELL, NEW YORK, N. Y.—Dr. Morton has studied 27 fetal pelves, carefully dissected and mounted by expert anatomists. This is a much larger series than Thompson's 8 cases and is the largest collection which has come to my attention. The dissection and mounting of fetal pelves and even the pelves of older children without distortion requires a great deal of expert care. I hope that more collections similar to Dr. Morton's will become available for study and that the pelves of children that come to autopsy will be thoroughly studied and that many of them will be preserved.

I agree with Dr. Morton that the measurements of the cardinal diameters in these very small pelves and especially in a small series have very little significance. It is the morphology of the pelvis as a whole which counts. The study of the pelvis in the live individual by external measurements is practically useless in describing the shape of the true pelvis.

His second approach is the use of the x-ray in studying the pelvis of the living individual. I have been amazed at the amount of detail and accuracy which can be obtained in carefully taken roentgen ray films, even in fetuses.

I wish Dr. Morton had not been so positive in his conclusions that sex variations before puberty are negligible. I do not think that contemporary anthropologists will agree with him in this statement. Dr. Wesley Dupertuis, after reading Dr. Morton's paper, made the following note: "As an anthropologist having worked in the laboratory of Dr. Hooton, and perhaps having been influenced by his ideas, I have always felt that it was possible to determine the sex in the pelves of children, infants, and perhaps those of fetuses. Certainly from the osteologic material that I have seen, there seem to be tremendous differences in the pelves of small children. From Todd's own material and from the impression that I have gained from Hooton and Hrdlicka's work, I believe that most anthropologists feel that pelvic sex differences are evident in early childhood and perhaps even in the intra-uterine period."

Six years ago we examined the pelves of 28 girls and 15 boys shortly after birth. Since that time we have examined a great many more pelves, both boys and girls, normal and abnormal. In view of Dr. Morton's statement, we have reviewed many of the cases and still feel that the conclusions published in the *American Journal of Roentgenology and Radium Therapy* (Vol. 41) are correct: "Fehling and Thompson have shown that many of the sexual differences as illustrated and described for the typical male and female pelves can be recognized in the fetal pelvis early in intrauterine life. Recently we have studied the roentgenologic appearance of the fetal pelvis shortly after birth. In addition to the recognition of sexual differences, we have observed variations in inlet shapes in the female child which suggest anthropoid and android types."

pocket gopher and the latter with rats, demonstrated that the pelves of castrate and noncastrate males could be made to assume female characteristics by the administration of an estrogen.

#### SUMMARY AND CONCLUSIONS

The direct study of 27 fetal pelves of various ages and the roentgenometric study of 143 children of both sexes, from 3 to 17 years of age, revealed interesting observations with regard to the development of the shape of the pelvic inlet and the development of sex differences in pelves.

The shape of the inlet was found to be broader than long at all periods of fetal life. There were no significant sexual differences. In children under six years of age the inlet was still either broader than long or round in most instances. From six to eleven years of age the pelvic inlet was invariably longer than broad. In all of the children of prepuberty age the outline of the pelvic inlet was not smooth but showed an inward bowing in the acetabular regions, presumably due to the upward thrust of the femora. This bowing was not present in the fetal pelves nor in the pelves of children in the postpuberty age group. After puberty the pelvic inlet of the female pelves showed a tendency to flattening, so that many of them again became broader than long. These changes were demonstrated in individuals by serial studies at two- to four-year intervals.

No significant sexual differences were observed in the fetal period, though the number of pelves was too small to exclude minor variations. In the years before puberty a comparison of the roentgenograms of male and female pelves (inlet view, side view, and subpubic arch view) revealed only two possible differences, to wit, a shorter posterior segment at the pelvic inlet in the male and a downward angulation of the sacrum in the male. After puberty the well-known characteristics of adult male and female pelves were observed. While it is impossible to deny categorically that differences do exist between the male and female before puberty, certainly the major differences appear at this time.

The finding of a common type of pelvis in fetal life and in children before puberty, both of which are different from adult types, and distinct differentiation after puberty, suggests that the sex hormones play a large role in the development of the final pelvic form, not only with regard to sexual differences but possibly also with regard to variations in pelves of the same sex. It cannot be denied, of course, that hereditary, nutritional, or possibly other as yet unknown, factors may play a role.

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Another point that attracted me was the fascinating possibilities that lie in continuing these studies over a considerable period of years in the same individual, following each one from infancy to adult life. Dr. Morton evidently intends to do this, having begun already to repeat some of his studies begun in children now growing older. When these children can be followed into adult life what are now plausible conjectures will be matters of record, no doubt.

DR. HERBERT THOMS, NEW HAVEN, CONN.—Recently Dr. Greulich and myself have concluded just such a study as Dr. Morton suggests. We have followed 107 orphanage girls for over four years through puberty, and have taken a roentgenogram of each girl at intervals of one year. I have lantern slides which almost duplicate those which Dr. Morton has shown. I would like simply to read our conclusions.

This study was based upon 107 orphanage girls on whom pelvic roentgenograms and anthropometric observations were repeated at intervals of approximately twelve months over a period of four years.

*Conclusions.*—a. The shape of the pelvic inlet is very similar in boys and girls up to the time of puberty.

b. Growth of the pelvis up to the time of puberty (so far as it can be followed in the anteroposterior film) is slow and symmetrical. During the prepuberal period the acetabular constriction is well marked.

c. At about the time of puberty in girls, usually just prior to the first menstruation, but sometime after the development of breasts has begun, a relatively rapid growth and remolding of the inlet occurs. This is usually completed within eighteen months to two years after the menarche. Thereafter very little growth or change in shape of the inlet was noted. It seemed to have attained practically its adult size and configuration.

DR. HOWARD C. MOLOY, NEW YORK, N. Y.—Dr. Morton's work brings up two important points. The first deals with the presence or absence of sexual differences in the pelvis of the fetus, infant, or child; the second concerns the changes in the morphology of the pelvis produced by growth and development quite distinct from the sexual characteristics in pelvises.

Six years ago, as Dr. Caldwell has stated, we obtained stereoroentgenograms on forty-three infants shortly after birth and from their study believed we recognized distinct sex differences thereby confirming the work of Fehling and Thompson both of whom reported the recognition of sex differences in young fetuses. Dr. Morton also recognizes sex differences in infants and children but believes these differences are too slight to warrant consideration. This introduces a controversy which we believe should be settled before theories are evolved in regard to the action of the growth hormones from the application of one or the other points of view. We shall attempt to obtain a repeat roentgenologic examination upon the original series of forty-three cases examined six years ago and report our findings because of the great importance of this particular point.

With regard to the second point, I believe Dr. Morton's paper represents an important contribution. We have also observed the acetabular bulging and have noted a great variation in the age limits for epiphyseal lines to form and disappear. The pelvis appears to increase in length through growth at the ilium, ischium, and pubis during the period of infancy and early youth. Later the sacrum increases in width to effect an increase in transverse diameters. However, this suggestion can be proved by only one method, the study of stereoroentgenograms obtained at intervals upon the same individual. This type of study requires many years to obtain significant information yet the question is important enough to warrant a beginning in several clinics.

Dr. Morton acknowledges that there are these sex variants but claims that they are not significant until after puberty. Of course the most significant changes are at puberty, but anthropologists believe that the sixth year, when the second teeth appear, is almost as important as puberty in the growth and development of the child. As Dr. Morton has said, it is about this time that the long transverse oval of the infantile pelvis changes into the long anteroposterior oval. It is the time also when the pushing forward into the pelvic cavity of the acetabulum begins to occur. Thyroid and other endocrine studies at this time would be interesting.

From Dr. Morton's own pictures, I have selected two cases which certainly are typical male and female pelves, as marked as in any individual adult. In Thompson's slides the differences are very marked. In our own which have been re-examined over and over again, the sex overlaps occur in both sexes and are easily determined. I agree with Dr. Morton on the position of the inlet in fetal life. I wish Dr. Morton would add one more picture to his series in order to study the pelvis from inlet to outlet by stereoscopic examination, for there is no doubt that for the study of the morphology of this pelvis from inlet to outlet the stereoscopic examination gives much more information than flat pictures. The precision stereoscope is not essential but it does reduce the amount of distortion and error.

Dr. Steele's paper which follows will point out some objections to Dr. Thoms' technique. Dr. Thoms' best pictures are obtained in the anthropoid type of pelvis, where it is easy to have the film parallel to the inlet. As the angle between the spine and the inlet decreases and becomes more acute, as in the android pelvis, it is difficult to have the film absolutely parallel with the inlet. A ten-degree variation in the inclination of the pelvis and the film completely distorts the forepelvis. I believe that is the reason that Dr. Thoms does not recognize the android pelvis and has left it out of his classification.

I hope Dr. Morton will continue his work and that more clinics will use x-ray techniques to study the development of the pelvis. Front, back, and lateral pictures of the child, with x-rays of the pelvis, preferably stereoscopic, should be taken at birth and possibly each year through puberty. Careful x-ray examinations of the pelvis, backed by adequate histories of the minor as well as the serious injuries, the various infections and diseases of the child, the metabolic deficiencies, and especially our constantly increasing information regarding the function of the endocrine glands will in time add to our knowledge of the etiologic factors which produce the complex osseous structure of the adult pelvis.

DR. PAUL TITUS, PITTSBURGH, PA.—Dr. Morton's outline of the general types of pelves found in fetal life and in infancy up to puberty was complete in every respect. I did not get Dr. Caldwell's impression that Dr. Morton intended to convey that there were no outstanding sexual differences between girls and boys before the period of puberty. It was my impression he stated that these changes do begin in that particular period but are more evident at the time of puberty and immediately following. Dr. Morton did say that all children show a general characteristic change in the shape of their pelves when they change from infancy into youth and he conjectured that these changes, platypelloid to a dolichopellic, result from trochanteric pressure on the sides of the pelvis from playing and running, as children do, while ossification is still incomplete.

As evidence of the correctness of Dr. Morton's conjecture I might recall to you the comments that Dr. Williams used to make as to the reasons for certain changes occurring in a coxalgic pelvis. He said that if the disease was on the left side the person would favor that side and strike harder on the sound right side. Hence the indentation of the pelvis would be on the side opposite the diseased hip, this being possible because ossification was still incomplete. That fits in very well, I think, with what Dr. Morton has said regarding the narrowing from side to side and the lengthening of the pelvic inlet.

## SOLUTION OF POSTERIOR PITUITARY SULFONATE (PIT-SULFONATE) IN LABOR\*

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**S**OLUTION of posterior pituitary U.S.P. when used before the end of the second stage of labor may cause tetanic contractions of the uterus with possible injury or death of the fetus or rupture of the uterus with possible death of the mother. In view of these dangers, obstetricians have refrained from the use of solution of posterior pituitary to hasten delivery. Some have used it to induce labor. Since the response of the uterus to the hormone is variable, the usual initial injection for inducing labor has been 0.03 c.c. (one-half minim) and every twenty minutes the dose has been increased by 0.03 c.c. to a maximum of 0.2 c.c. (three minims). As soon as the patient is having contractions of thirty seconds or more duration, at intervals of three to five minutes, its use has been discontinued. The total amount used is 1 c.c. This is obviously a time-consuming procedure but is a relatively safe method for preventing tetanic contractions of the uterus. However, one of us has seen 5 patients who had uterine ruptures from posterior pituitary solution. One patient had 0.3 c.c. and died, another had 0.12 and died, while of the others each had 0.12 c.c. and recovered.

Many patients are delivered by general practitioners who believe that they can hasten delivery by injecting solution of posterior pituitary, without any danger to the mother or baby. This procedure may be dangerous even when the cervix is completely dilated. In these cases the obstetrician believes that the delivery is effected with less danger by means of the forceps. The general practitioner has fairly valid reasons why he does not use the forceps; thus, many of his deliveries are at the home and he has either forgotten the forceps or they are not sterile, and he is alone.

Realizing these dangers from solution of posterior pituitary, several pharmaceutical houses combined the posterior pituitary hormone with other glandular extracts. Of these, the thymus was the one most frequently used. Injection of these combined pituitary and thymus extracts during labor were said to be without danger to mother or baby. DeLee recently stated that the consensus of opinion of obstetricians who have

\*Read at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.

DR. JOSEPH L. BAER, CHICAGO, ILL.—There is a pelvic factor which I should like very much to have the essayist touch upon in his closing remarks, namely pelvic inclination. This is one of the important osseous components with which we are concerned.

I believe that 20 to 25 per cent of displaced uteri are displaced because of the defective pelvic inclination which that group of women exhibit. The gross sagittal section of the pelvis in women with uterine displacements shows that the promontory is at a much higher level in relation to the symphysis than in the normal mature female. There is a vertical wall posteriorly, as the essayist showed, for the sacrum undergoes no curvature during fetal life.

DR. FREDERICK H. FALLS, CHICAGO, ILL.—I am very much impressed with Dr. Morton's contribution, particularly as it is based on actual measurements of the dissected specimens of the pelvis and believe this is the way we are going to get information that will last rather than by x-ray pictures. After all, x-ray pictures are shadows and they are none too reliable, even though we have gone a long way toward making measurements from those shadows more reliable by our modern methods of mensuration.

The second thing that impressed me was that this work may explain the dystocias that occur in very young women who are in labor. It has been difficult to see why some of these patients have so hard a time, and this inward bowing of the sides of the inlet of the true pelvis, which would be very difficult to detect clinically, may be the explanation.

If you look at the pregnant woman as a whole you can tell from the general conformation what type of labor she is likely to have. For example, a short, stubby fingered individual, with short femurs, will also have a contracted pelvis. The hormones developing at puberty have a marked effect in bringing about this change.

DR. MORTON (Closing).—I admit freely that the question of the sex differences is still a matter of controversy and certainly 27 pelves are not a sufficient number upon which to base definite conclusions. Fehling's study was based upon 130 fetal pelves and was very detailed and rather convincing. On the other hand, I should like to refer you to the recent study of Yamamura. This author reported an extremely detailed study of 140 fetal pelves, in which all the measurements and indices were handled statistically. While Yamamura seems to have accepted Fehling's general thesis, careful inspection of his figures reveals that there were numerous points of disagreement. Furthermore, Yamamura's figures revealed only one sexual difference which could be said to be statistically significant. The finding referred to was the closer proximity of the greatest transverse diameter of the inlet to the sacrum in the male. You will recall that our roentgenologic study of children's pelves showed a similar statistically significant difference. These facts may indicate that sex changes *do* start at a very young age. However, I do feel that the major changes appear at puberty and do not believe that the problem of whether there are any sex differences at all before this time can be settled until we have studied this question in more detail.

You are all probably familiar with the experimental work on the effects of hormones on the bony pelvis in animals. Hisaw working with the pocket gopher, and Corner with rats, demonstrated that in both castrate and noncastrate male animals the bony pelvis could be made to take on female characteristics by the administration of estrogenic substances. These results constitute rather convincing evidence of the effect of the sex hormones upon the growth and development of the pelvis.



the standard hormone. These results are what one would expect because to obtain the proper dose for the small animals the solution of pit-sulfonate had to be diluted five hundred times, thereby resulting in the immediate freeing of the pituitary hormone.

In intact anesthetized cats and guinea pigs, the results are shown in Table II.

TABLE II

| SUBSTANCE                         | NUMBER OF TESTS | MEAN LATENT PERIOD MIN. | MEAN TIME TO PEAK EFFECT MIN. | MEAN TOTAL DURATION MIN. | MEAN LATENT PERIOD MIN. | MEAN TIME TO PEAK EFFECT MIN. | MEAN TOTAL DURATION MIN. |
|-----------------------------------|-----------------|-------------------------|-------------------------------|--------------------------|-------------------------|-------------------------------|--------------------------|
| Standard lot of pituitary extract | 3               | 5                       | 80                            | 373                      | 3                       | 20                            | 60                       |
| 124                               | 3               | 4                       | 60                            | 400                      | 2                       | 12                            | 48                       |
| 125                               | 3               | 4.5                     | 60                            | 347                      | 3                       | 17                            | 52                       |

With all three samples the rate of oxytocic and pressor action is about the same. Thus, in comparison with the control, the medicated samples show no delayed or prolonged action.

On the blood pressure of 12 anesthetized cockerels, intramuscular injection of the three samples failed to produce any change in the blood pressure. Intravenously, however, there was a characteristic decrease in blood pressure. As would be expected, by vein all three samples gave the same action without a difference in the duration of action.

The undiluted pit-sulfonate was used in the experiments for determining the oxytocic and pressor values in cats, guinea pigs, and cockerels. However, the doses varied from 0.2 to 0.3 c.c. per kilogram of cat and 0.5 to 1.5 c.c. per kilogram of guinea pig and cockerel. The oxytocic dose in the human ranges from 0.03 to 0.3 c.c. and the antidiuretic from 0.1 to 1.0 c.c. Comparable doses in a 60 kilogram woman would be 1.8 to 20.0 c.c. for the oxytocic and 6.0 to 60 c.c. for the antidiuretic. The comparatively huge doses used in the animals would contain enough free hormone to mask the action of the pit-sulfonate.

Studies on the human subject with the drug given intramuscularly or subcutaneously have shown striking differences from the solution of posterior pituitary. A patient with diabetes insipidus was given 0.5 c.c. doses every twelve hours of either posterior pituitary or pit-sulfonate with results as shown in Table III.

TABLE III

| MEDICATION          | INTAKE, C.C. - PER 24 HOURS - URINE, C.C. |       |
|---------------------|---|-------|
| None                | 9,480                                     | 9,690 |
| None                | 13,380                                    | 9,180 |
| Posterior pituitary | 3,240                                     | 1,740 |
| Pit-sulfonate       | 2,100                                     | 600   |

used these substances is that these solutions merely contained less of the posterior lobe hormone than the standard solution.

We believe that if the hormone from the posterior lobe of the pituitary could be combined with some other substance, so that it would be liberated very slowly, the dangers would be minimized or eliminated. We have found that the posterior pituitary principle can be precipitated from an aqueous solution with the aid of high molecular weight sulfonic acids. The best reagents appear to be the anthraquinone sulfonic acids or their amides and of these the anthraquinone 2.6 disulfonic acids appear to be the best. These combinations with the posterior pituitary hormone may be suspended in water or peanut oil and are quite suitable for use. This report deals with the product obtained by precipitating the posterior pituitary hormone with anthraquinone 2.6 disulfonic acid, and suspending the latter in a 0.5 per cent solution sodium-anthraquinone 2.6-disulfonic acid. The resultant product, solution of posterior pituitary sulfonate, which for the sake of brevity we have called pit-sulfonate, has an acid reaction. The posterior pituitary hormone is liberated when the solution becomes alkaline. This would happen immediately if the solution were injected intravenously. If injected subcutaneously or intramuscularly, the pituitary hormone is liberated slowly. There is a very small amount of the active hormone in solution and if large amounts of pit-sulfonate are injected, the free hormone will give the usual early pituitrin reaction, thus tending to mask the response of the new substance.

Experiments with pit-sulfonate on uterine strips showed no difference from solutions of posterior pituitary. Therefore, its oxytocic content is equal to that of the solution of posterior pituitary. Since the strips were immersed in a buffered solution and since the pituitary hormone is set free on neutralization, this result is what one would expect.

Experiments carried out at the Lilly Research Laboratories by Doctors Chen and Swanson yielded the following results:

Samples 124 and 125 of pit-sulfonate were tested for delayed anti-diuretic potency in rats by the Burn Method. The results are shown in Table I.

TABLE I

| SUBSTANCE                            | NUMBER<br>OF<br>RATS | MEAN TOTAL<br>AT MAXIMUM<br>RATE<br>C.C. | MEAN TOTAL<br>AT END<br>OF TEST<br>C.C. | DURATION<br>OF<br>TEST<br>MIN. |
|--------------------------------------|----------------------|--|---|--------------------------------|
| Standard lot of<br>pituitary extract | 12                   | 14.05                                    | 27.5                                    | 192                            |
| 124                                  | 12                   | 14.56                                    | 28.0                                    | 189                            |
| 125                                  | 12                   | 14.10                                    | 28.6                                    | 183                            |

As shown in Table I, all three tests are approximately the same. Thus, in comparison with the control, the medicated samples did not show a retention of urinary excretion. The antidiuretic value is the same as

new product does not manifest itself as early as the posterior pituitary. However, its action consistently lasts longer, as depicted in Fig. 2.

Fig. 3 illustrates the effect of posterior pituitary and pit-sulfonate on the same human pregnant uterus. The pressure changes were determined by an intrauterine bag. It is obvious that the posterior pituitary had a much shorter latent period and resulted in definite tetany.

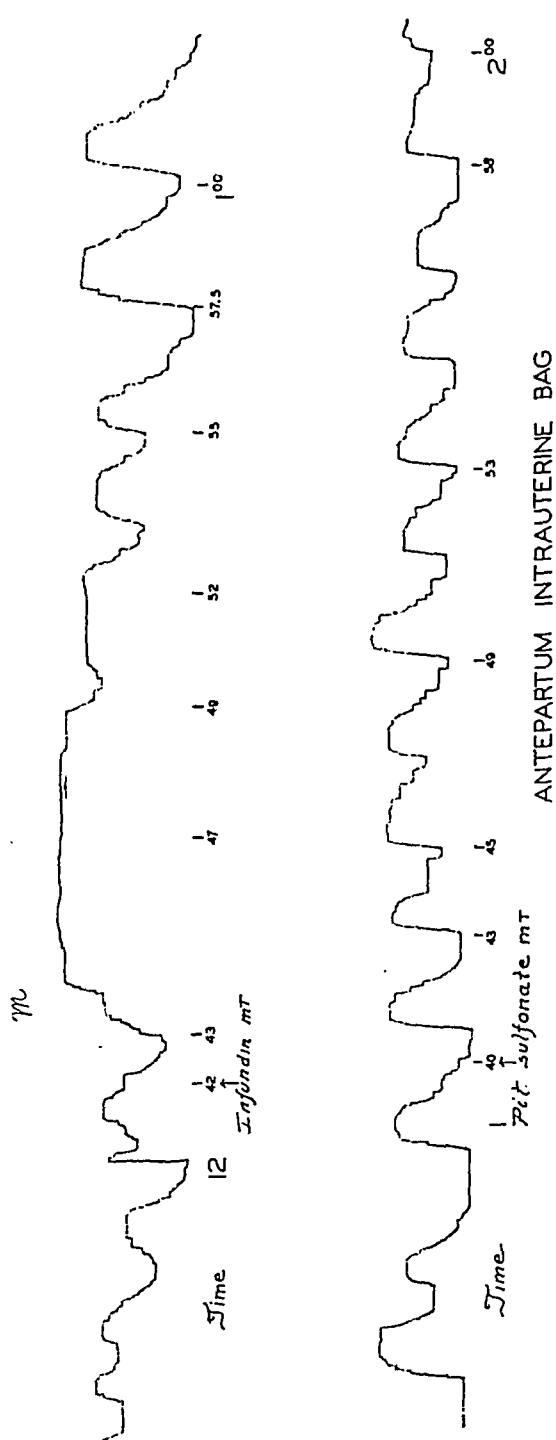


Fig. 3.—Recording of contractions of pregnant uterus. Posterior pituitary and pit-sulfonate were injected in the same patient.

Pit-sulfonate although of the same strength as the standard solution, had a more marked antidiuretic effect, because it was liberated slowly, thus prolonging its action.

Data from the same patient comparing identical doses of the standard and new product are illustrated in Fig. 1. As would be expected,

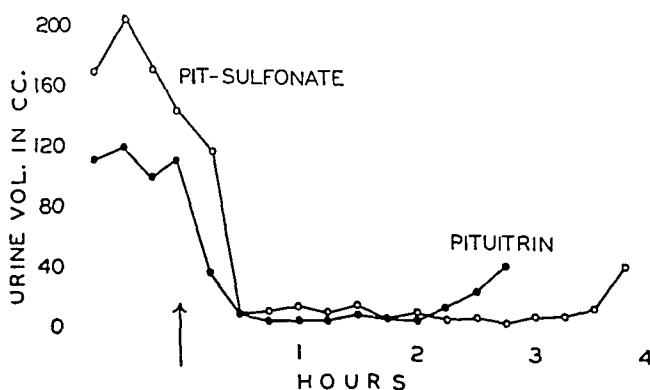


Fig. 1.—Graphs showing the antidiuretic effect of 0.06 c.c. of solution posterior pituitary and 0.06 c.c. of pit-sulfonate in a patient with diabetes insipidus. Two hundred cubic centimeters of water were taken every thirty minutes. The arrow indicates time of injection.

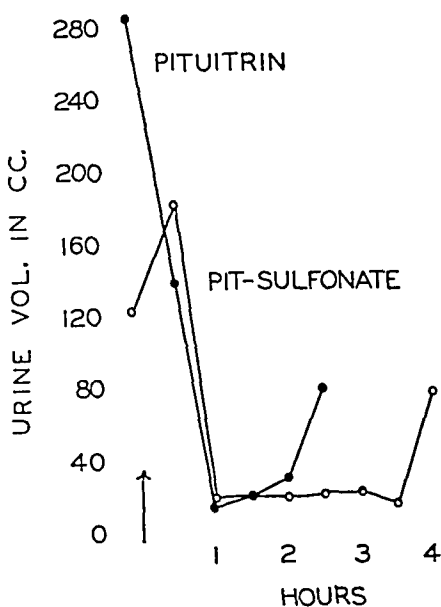


Fig. 2.—Graphs showing the antidiuretic effect of 0.06 c.c. of solution posterior pituitary and 0.06 c.c. of pit-sulfonate in a normal subject. One thousand cubic centimeters of water were taken one hour before the injection.

the solution of posterior pituitary caused a decrease in the urine output earlier than the pit-sulfonate. However, the latter compound had a much more prolonged action.

Similar amounts of pit-sulfonate and posterior pituitary were given subcutaneously to one of us (W. J. D.). The antidiuretic effect of the

pituitary or pit-sulfonate; (2) the duration of the first contraction; (3) the length of time over which these products were active; and (4) the fetal heart rate.

Data for the latent period are given in Table IV. The statistical analysis of the pit-sulfonate data are based on the latent periods from one to twenty minutes. The mean for solution of posterior pituitary is 5.2 minutes, while the mean for pit-sulfonate is 12.8 minutes. If the

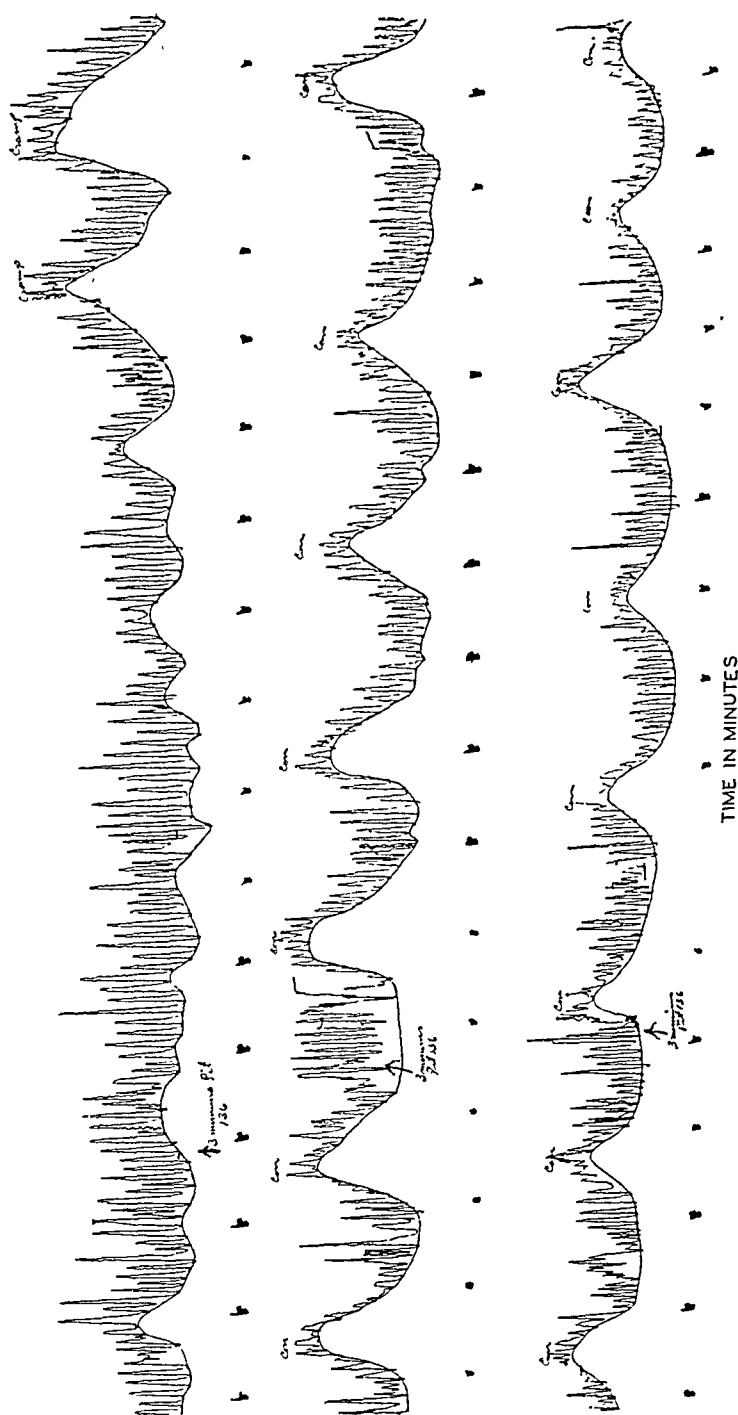


Fig. 5.—Hystero-graph of Fenning. Contractions of pregnant uterus after repeated injections of pit-sulfonate. The fine lines are due to maternal respiratory movements, and the course waves are caused by uterine contractions.

The new product resulted in an increased tonus but there were always very definite contractions. Similar studies were made in 23 patients. The difficulty with this method of study lies in the fact that the susceptibility of the uterus to posterior pituitary parallels the time the bag is in the uterus. Thus, the latent period would be shorter and the contractions stronger at the end of four hours than at the end of one hour.

Numerous studies were made by Fenning, Associate Professor of Pharmacology and Physiology, University of Utah, with his capacigraph, an instrument which records uterine contractions, but has no connection with the patient. Sixty-five patients at term were given solutions of posterior pituitary or pit-sulfonate. Fig. 4 illustrates the effect of posterior pituitary solution and of pit-sulfonate. The uterine tetany and shorter latent period with pituitary are obvious. Fenning concluded that pit-sulfonate has a latency and overall action approximately two times that of solution of posterior pituitary.

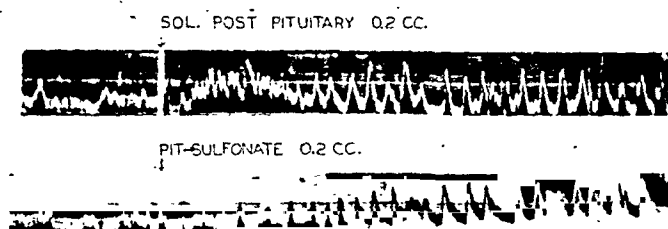


Fig. 4.—Capacigraph of Fenning. Contractions of pregnant uterus after injections of posterior pituitary and pit-sulfonate in different patients. Time interval is the same.

Studies with the Fenning hysterograph are shown in Fig. 5. Repeated 0.2 c.c. doses of pit-sulfonate resulted in an increased amplitude and frequency of the contractions without the development of uterine tetany in a patient who went on to delivery within three hours.

Fig. 6 illustrates the effect of pit-sulfonate on the post-partum uterus. Rhythmical uterine contractions began twenty-five minutes after the injection and were still present at the end of five hours. Posterior pituitary has a much shorter latent period.

This work was started in April, 1938, and our problem has been to determine if pit-sulfonate had any actions which were different from those of the solution of posterior pituitary on the human pregnant uterus. Careful observations were made on pregnant patients at term who were either having labor induced or were having very irregular contractions. The early studies were all made by one of us (W. J. D.). Subsequent observations were made by the residents and internes under supervision of one of us (W. J. D.).

We were interested in determining the following: (1) the latent period before a uterine contraction begins after the injection of posterior

pituitary. The latent periods of two to six minutes with the pit-sulfonate are the result of the minute amount of the pituitary hormone which is in solution. In an endeavor to eliminate these early contractions studies of pit-sulfonate in oil are now in progress.

TABLE IV. LATENT PERIOD OF ANTE-PARTUM SUBCUTANEOUS INJECTIONS

| LATENT PERIOD<br>MINUTES | SOLUTION<br>POSTERIOR PITUITARY | PIT-SULFONATE |
|--------------------------|---------------------------------|---------------|
| 1-2                      | 2                               | 1             |
| 3-4                      | 10                              | 9             |
| 5-6                      | 11                              | 17            |
| 7-8                      | 2                               | 14            |
| 9-10                     | 1                               | 38            |
| 11-12                    |                                 | 54            |
| 13-14                    |                                 | 24            |
| 15-16                    |                                 | 22            |
| 17-18                    |                                 | 14            |
| 19-20                    |                                 | 21            |
| 21-26                    |                                 | 11            |
| 27-32                    |                                 | 9             |
| 33-60                    |                                 | 11            |
| Total cases              | 26                              | 245           |
| Mean                     | 5.2 minutes                     | 12.8          |
| Standard error           | 0.34                            | 0.31          |
| Standard deviation       | 1.76                            | 4.67          |

Certain patients showed increased uterine tonus but in over 245 patients with one to five injections each, none had uterine tetany to a degree that caused any concern about fetus or mother. The initial contractions lasted from ten seconds to one minute. One doctor on the courtesy staff stated that his patient had marked uterine tetany but there is no corroboration of his observation. On many patients treated by one of us (W. J. D.) each dose of pit-sulfonate was 0.3 c.c. (five minims) with no evidences of tetany. A similar amount of posterior pituitary solution almost invariably produces uterine tetany.

The duration of action was difficult to measure and could only be estimated. If we use posterior pituitary for the induction of labor, the injections are given every twenty minutes but with pit-sulfonate the intervals are usually forty to sixty minutes.

TABLE V. LATENT PERIOD OF ANTE-PARTUM SUBCUTANEOUS INJECTIONS IN SAME PATIENTS

| NUMBER | POSTERIOR PITUITARY<br>MINUTES | PIT-SULFONATE<br>MINUTES | DOSE<br>C.C. |
|--------|--------------------------------|--------------------------|--------------|
| 204502 | 5                              | 10                       | 0.06         |
| 212400 | 2                              | 8                        | 0.06         |
| 206181 | 2                              | 10                       | 0.06         |
| 206181 | 3                              | 7                        | 0.2          |
| 215241 | 2                              | 2                        | 0.06         |
| 215241 | 1                              | 3                        | 0.06         |

The fetal heart rate might decrease twenty to thirty beats per minute if the initial contraction lasted one minute, but there was no evidence

latent periods over twenty minutes were included, this figure would be larger. All of the latent periods for posterior pituitary were less than ten minutes and 88 per cent were less than seven minutes. Sixty-eight per cent of the latent periods for pit-sulfonate were over ten minutes and twelve per cent were over twenty minutes. It is apparent that there is a marked variation in the latent period but this is what one would expect since patients vary in their susceptibility to posterior

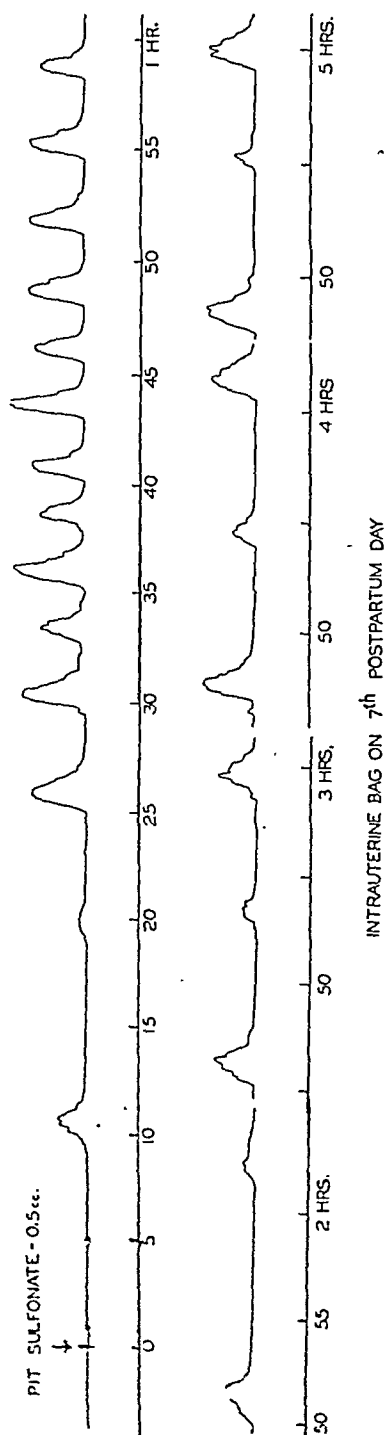


Fig. 6.—Recording of contractions after an injection of 0.5 c.c. of pit-sulfonate.



Fig. 7 illustrates the tetany produced by posterior pituitary as compared with a larger amount of pit-sulfonate.

Observations by Murphy on M. B., a primipara, at term, 4 cm. dilatation, having irregular contractions were as shown in Table VI.

TABLE VI

| LATENT PERIOD<br>MINUTES | TIME<br>MINUTES |  |
|--------------------------|-----------------|--|
|                          | 0               | 0.2 c.c. pit-sulfonate                         |
| 12                       | 12              | Uterine contractions and slight abdominal pain |
|                          | 24              | 0.2 c.c. solution of posterior pituitary       |
| 5                        | 29              | Uterine contractions and abdominal pain        |
|                          | 31              | 0.3 c.c. pit-sulfonate                         |
| 11                       | 42              | Uterine contractions and abdominal pain        |
|                          | 49              | 0.3 c.c. solution of posterior pituitary       |
| 6                        | 55              | Uterine contractions and abdominal pain        |
|                          |                 | Patient delivered 12 hours later               |

Doses of pit-sulfonate of 0.2 to 0.3 c.c. have been used during the second stage in six primiparas and fourteen multiparas. No tetanic contractions were produced and there were no significant alterations in the fetal heart rate.

We do not advocate any type of posterior pituitary hormone to hasten delivery, but we believe that we have accomplished our objective which was to produce a compound of the posterior pituitary hormone which could be used by the physician with much less danger to mother and fetus.

We have purposely omitted any data pertaining to the per cent of patients in whom labor was successfully induced because our only purpose was to prove that we had altered to some degree the properties of the solution of posterior pituitary U.S.P.

#### CONCLUSION

Subcutaneous or intramuscular injections in pregnant women at term of solution of posterior pituitary sulfonate differ from the usual solutions of the posterior pituitary hormone in that the latent period is longer, there is little, if any, likelihood of tetanic contractions of the uterus, and the duration of action is longer.

We are indebted to the following for pertinent data: Drs. K. Chen, E. Swanson, Con Fenning, S. Gardner, D. Murphy, and Albert Holman.

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#### DISCUSSION

DR. ALFRED C. BECK, BROOKLYN, N. Y.—My lack of experience with this particular preparation will not permit me to say anything either for or against it. A wide experience with the use of posterior pituitary extract, however, enables me

at any time of fetal asphyxia. Recovery was always rapid and complete. Attempts were made to obtain graphic records of the fetal heart sounds but the changes in the abdominal contour during uterine contractions caused the microphone to move, producing so much noise that we were unable to obtain satisfactory records. Our studies are all based on periodic counts made by auscultation. The can of ether and mask are no longer kept at the patient's bedside during induction of labor with pit-sulfonate. There were no fetal deaths or injuries to fetus or mother.

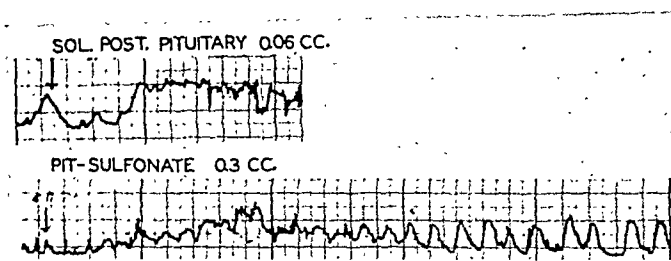


Fig. 7.—Tocograph of Lorand. Contractions of pregnant uterus after injection of 0.06 c.c. of posterior pituitary and 0.3 c.c. of pit-sulfonate in different patients. Time interval is the same. (Courtesy D. P. Murphy.)

Data in Table V illustrates a comparison of the two substances on the same patients. The difficulty here again lies in the fact that the uterus, as a rule, is more susceptible to the second injection than to the first. Therefore, three of these patients had posterior pituitary first and the other three had pit-sulfonate first. It is apparent that with but one exception, the latent period for the pit-sulfonate was much longer than that for posterior pituitary.

Dr. Albert Holman, who induces labor in many patients with posterior pituitary solution has used pit-sulfonate in over two hundred cases. The injections and observations were all made by one person who has been doing this work for years. Holman states that with posterior pituitary it required 8 to 12 doses at thirty-minute intervals to induce labor while with pit-sulfonate only 3 to 5 doses at sixty-minute intervals are required. The latent period for posterior pituitary according to him is two to four minutes while with pit-sulfonate the latent period is ten minutes with the maximum contraction occurring in about thirty minutes after the injection. He states that they observed no stormy or tetanic contractions of the uterus and that the contractions which occurred after pit-sulfonate simulated those of normal labor much more closely than those produced by solution of posterior pituitary.

Studies of the effect of pit-sulfonate on the post-partum uterus were made at the University of Michigan by Dr. S. Gardner. He states that the latent period is ten to twenty minutes. It produced large rhythmical contractions which lasted from fifty minutes to four hours and forty-five minutes. The action of the pit-sulfonate according to him was much longer than that obtained with solutions of posterior pituitary. He thinks it is similar in action to the oral or intramuscular action of the whole alkaloid of ergot or ergonovine.

Experiments with pit-sulfonate have also been carried out, using the Lorand tocograph at the University of Pennsylvania by Dr. D. Murphy.

advantages would be a very useful addition to an obstetrician's equipment. And while we believe the abuse of ecbolics may do immense harm, we still feel there is a place for their careful and skillful use. A new preparation like pit-sulfonate will perhaps be safe only when used with the same caution and care that should be exercised when using pituitrin. The unhappy results of the abuse of pituitrin may protect the reputation of the newer preparations as they are developed.

DR. WILLIAM R. NICHOLSON, PHILADELPHIA, PA.—I have been greatly interested in this paper because I have always believed in pituitrin, as the last speaker said, if it is used in the right way. It has always seemed to me that one might just as well say that strychnine or morphia must not be used because fatal harm can be done with them in overdoses as to condemn pituitrin completely for obstetric use. I have yet to see a case in which there was a tetany of the uterus with the dose that I insist upon as an initial dose, that is, one minim. I have of course seen tetany of the uterus in the old days when so-called "surgical pituitrin" first came out which was double the strength of the present "obstetric pituitrin" and when the initial dose was larger.

I have probably used pituitrin a little more generally and with less strict indications than some of those who have spoken today. I have used it to stimulate sluggish contractions, even though the cervix was not more dilated than three or four fingers, but it was given only in small doses and at proper intervals.

DR. JOSEPH L. BAER, CHICAGO, ILL.—With complete deference to Dr. Nicholson, I must say that we have seen tetany of the uterus follow one minim of pituitrin and with death of the fetus in utero. Moreover, there is the risk that the nurse may misread the order and give an ampoule instead of a minim. That has happened, I confess with humility, in our institution. I hope that Dr. Dieckmann, if this product is to be put on the market, will see to it that it is put out in one minim doses per ampoule. I offer the suggestion to the pharmaceutical firms that they put out their pituitary drugs in two groups, 1 c.c. ampoules for hemorrhage only, and one minim in ampoules for induction of labor.

DR. DIECKMANN (closing).—We do not use pituitrin to hurry labor or delivery. I have used this drug on 6 primiparas and 14 multiparas with complete dilatation and the head on the floor. Most of these were private patients. There was no abnormal slowing of the fetal heart rate and no uterine tetany. I believe this drug will be of value to the obstetrician for the induction of labor. I do not believe the general practitioner should use any form of pituitrin to hurry delivery, but if he is going to use an oxytocic, I believe pit-sulfonate is less likely to cause damage to the mother or fetus than pituitrin. Before it is released, it will be given extensive trials by obstetricians.

to discuss Dr. Dieckmann's paper and comment on his endeavor to diminish the risks associated with this powerful uterine stimulant.

We began to use posterior pituitary extract soon after it was introduced in this country. At that time it was given to almost every woman soon after the cervix was fully dilated. This use of the drug not only shortened the second stage of labor but it so reduced the need for forceps extractions that obstetric forceps were threatened with extinction. After several years, however, we began to attribute some of our fetal deaths to the use of this new drug. These bad results, together with the frequent reports of rupture of the uterus which appeared in the literature, led us to become more cautious and the use of posterior pituitary extract was restricted to those cases in which the requisites for forceps were fulfilled and an indication for forceps extraction had arisen. Thus because of an occasional bad result, an excellent addition to our armamentarium was almost abandoned.

Even when the drug was given in very small doses these dangers, as Dr. Dieckmann has noted, could not be eliminated. I recall one instance in which a multipara, who entered the hospital because she thought she was in labor, was given one minim of posterior pituitary extract to induce labor after a night's sleep. Within a few minutes the uterus began to contract violently. In spite of the fact that the patient was immediately anesthetized with chloroform, the fetal heart rate dropped to 80 and became irregular. Fortunately she delivered within twenty minutes and, although the child was deeply asphyxiated, it survived.

If one minim of the drug can cause such violent and prolonged contractions, the caution which we employed with regard to its use was certainly justified. On the other hand, were we justified in abandoning the use of this drug just because of the occasional difficulties which followed its use?

Dr. Dieckmann and his associates not only have not abandoned the use of posterior pituitary extract, but they have sought to lessen its dangers by altering its composition so that its absorption might be delayed. That they have been successful seems to be evident from the results of their investigations. That the delay in absorption will diminish the risk also seems to be evident from the results of its clinical application in a fair number of cases.

If further experience confirms these early observations, their work will restore to general usefulness a drug which once was considered a boon to obstetrics, and the elimination of its dangers not only will justify its use in the second stage but will make posterior pituitary extract invaluable in the treatment of the troublesome cases of first stage inertia.

DR. GEORGE KAMPERMAN, DETROIT, MICH.—The small amount of pit-sulfonate placed at our disposal by Dr. Dieckmann was of course not adequate for any conclusive observations. The five cases in which this drug was used were all cases of uterine inertia. In all these pains had lagged and although some dilatation had resulted, progress was exceedingly slow. However, enough dilatation was present to make a positive diagnosis that labor was actually in progress.

In these few cases the results as reported by the essayist were borne out. The latent period was longer than when pituitrin is used, approximately about twelve minutes passing before the change in pains was noted. This increase in pain was noted in 4 out of 5 cases. In no case was any tetanic contraction observed nor were contractions stimulated that caused a hasty or tumultuous termination of labor. The contractions seemed like normal uterine contractions and no fetal heart change was noted, and no baby was born with symptoms of distress.

We are in accord with the opinion that ecbolics are rarely necessary in normal labor, and should be used only when contractions are weak, and no obstruction exists. Never should they be used merely to hasten the termination of labor. But we do believe that a drug that could mildly stimulate uterine contractions without dis-

of irradiation treatment of 442 patients for uterine carcinoma. The cases reported in this series included only the more serious injuries with symptoms requiring active treatment or surgical intervention. Reporting from England in 1938, Todd<sup>2</sup> stated that the incidence of irradiation intestinal complications following treatment of uterine carcinoma was approximately 5 per cent in all clinics. His statement was based upon his knowledge of the results of treatment at the Christie Hospital and Holt Radium Institute in Manchester, the Marie Curie Hospital in London and the Radiumhemmet in Stockholm. His statistics probably included only the more severe types of injuries. In 1941, Chydenius,<sup>3</sup> of Helsingfors, reported an incidence of 10.2 per cent of intestinal strictures that followed irradiation therapy for uterine carcinoma in a series of 321 cases treated from 1937 to 1940.

The purpose of this report is to record our experience in the diagnosis and treatment of intestinal irradiation injuries at the Woman's Hospital from 1937 to 1941, inclusive. This recent five-year period was selected because we believe that during this time, data were recorded that give us the true incidence of intestinal injuries which developed following the technique of irradiation therapy employed. It is within this time that members of our staff have become aware of the frequency of occurrence of these intestinal lesions and that they produce characteristic symptoms and physical findings by which they can be diagnosed.

Irradiation injuries usually manifest themselves with the onset of intestinal symptoms, such as abdominal pain, frequent bowel movements, rectal tenesmus, and passage of varying amounts of blood and mucus by rectum. In some cases, the initial symptoms are those of intestinal obstruction, that is, abdominal pain, anorexia, nausea, vomiting, and obstipation or obstipation alternating with diarrhea. When these symptoms appear, they may be due to a temporary partial intestinal obstruction caused by hyperemia, edema, and spasm of the bowel at the site of an intestinal ulcer or to a true organic stricture resulting from the formation and contraction of scar tissue as Nature attempts to heal the injured bowel. Symptoms of an intestinal injury may develop at any time from immediately following irradiation therapy to within several months or years later.

Diagnosis of an irradiation injury is made by various means, including direct inspection of rectal and sigmoidal lesions through a sigmoidoscope, roentgen studies of the bowel and microscopic studies of biopsy specimens or of tissue removed at operation or at autopsy. Repeated examinations over a considerable period of time may be necessary to establish the diagnosis of an intestinal irradiation injury in any case under observation. Without careful diagnostic studies, it is impossible to be certain that symptoms suggesting the development of such injuries are not due to functional bowel disturbances, indiscretions in diet, too much catharsis or possibly conditions resulting from the malignant processes for which treatments were given.

## INTESTINAL INJURIES RESULTING FROM IRRADIATION TREATMENT OF UTERINE CARCINOMA\*

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*(From the Clinic of the Woman's Hospital)*

**M**OST of our knowledge and experience in the use of irradiation therapy for the treatment of uterine carcinoma has been acquired in the past twenty-five years. Within this time, reports from various excellent clinics throughout the world have appeared, describing a variety of techniques for radium and roentgen ray therapy and presenting statistical summaries of the results that have been obtained.

Although there is still some difference of opinion as to optimum amounts of irradiation to be used and the safest and most effective methods for its application, in general it may be stated that irradiation therapy for uterine carcinoma has become fairly well standardized.

Recognizing the value of this form of therapy and the risks involved in its use, gynecologists strive to meet two objectives, namely:

1. To deliver an amount of irradiation which can now be determined with reasonable accuracy as sufficient to destroy the malignant process provided it is radiosensitive and is confined to the uterus and its parametrial supporting structures.
2. To protect adjacent anatomic structures, and especially the urinary and intestinal tracts, against excessive secondary irradiation effects which may be destructive to their substance and function.

In reporting the results of therapy, it has been customary to record facts regarding the effect of irradiation on the progress of the disease and the survival rates of patients treated. Until recent years relatively little has been written regarding the undesirable and occasionally dangerous secondary effects of irradiation on the surrounding healthy tissues.

The few reports in medical literature regarding such complications have given detailed clinical and pathologic descriptions of some of the serious intestinal injuries that have been observed. They have also included discussions as to the probable causes of such injuries, but as a rule have provided little information as to the frequency of their occurrence.

However, in 1937, Corseaden, Kasabach and Lenz<sup>1</sup> reported an incidence of 8.7 per cent of intestinal injuries which occurred as a result

\*Read at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.

Within the five-year period covered by this report 6 patients in addition to the 32 listed in Table I came under treatment for intestinal strictures. As irradiation therapy for carcinoma of the cervix uteri had been carried out in all of these cases by members of our attending staff with the same techniques which are employed in our cancer clinic, it was decided to include them in the series of cases to be reported. By doing so the number of patients with intestinal irradiation injuries was increased to 38. Of the 38 cases, 29 had postirradiation intestinal strictures.

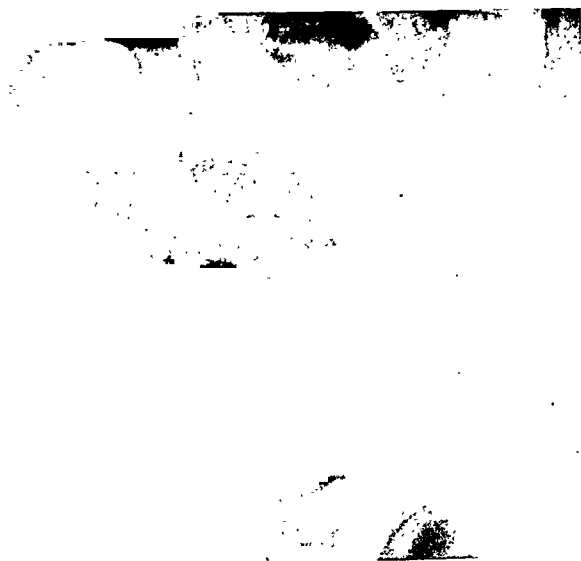


Fig. 1.—Mrs. S. (Hospital No. 74084), aged 35 years, was treated for adenocarcinoma of cervix with 4,200 mg. hr. of radium delivered in twenty-four hours. Intestinal symptoms began immediately after radium therapy. No roentgen therapy was used. Intestinal stricture was diagnosed at three weeks after radium treatment. Patient still has intestinal symptoms at one year and three months after irradiation therapy. *Comment:* Intestinal stricture was probably due to hyperemia, edema, and intestinal spasm at site of injury.

Table II is a summary of the diagnoses made in the 38 cases. It will be noted that the series included only one case of adenocarcinoma of the corpus uteri. Of the 37 patients with tumors of the cervix uteri, 4 cases were diagnosed as adenocarcinomas and 33 as squamous cell carcinomas. Table II also shows the distribution of the 38 cases of uterine carcinoma in accordance with the Ewing classification as to cell type.

Our own observations are in agreement with previously published reports<sup>1, 2, 4</sup> that intestinal complications resulting from irradiation injuries are due to three characteristic types or degrees of tissue reaction depending upon the location and extent of the original injuries. These include:

1. An acute localized proctitis or proctosigmoiditis.
2. Ulceration of the mucosa and wall of the intestine.
3. Formation of varying amounts of perirectal fibrous tissue.

Any one or a combination of these types of tissue reaction may develop in the same patient.

As a check on the extent of a malignant growth, irradiation therapy is preceded, in our clinic, by routine examinations of the lower bowel and urinary tract.

In Table I, it will be noted that:

1. 16.9 per cent, or approximately one out of every six patients treated for uterine carcinoma, developed some degree of proved injury to the intestine.

2. Only one intestinal injury occurred following treatment of 47 patients for carcinoma of the corpus uteri.

3. Of 142 patients treated for carcinoma of the cervix uteri, 31 developed postirradiation intestinal injuries including 23 intestinal strictures. In other words, an intestinal injury developed in one out of every 4 to 5 cases treated for carcinoma of the cervix, and one out of approximately every 6 patients treated had a postirradiation intestinal stricture.

TABLE I. TYPE AND INCIDENCE OF INTESTINAL IRRADIATION INJURIES THAT OCCURRED DURING TREATMENT OF 189 CASES OF UTERINE CARCINOMA AT THE WOMAN'S HOSPITAL FROM 1937 TO 1941, INCLUSIVE

| DIAGNOSIS IN CASES TREATED | NO. OF CASES | INTESTINAL LESION RESULTING FROM INJURY |                         |           |       |
|----------------------------|--------------|---|-------------------------|-----------|-------|
|                            |              | PROCTO-SIGMOIDITIS                      | ULCER WITHOUT STRICTURE | STRICTURE | TOTAL |
| Carcinoma of corpus        | 47           | 1                                       | 0                       | 0         | 1     |
| Carcinoma of cervix        | 142          | 5                                       | 3                       | 23*       | 31    |
| Total cases treated        | 189          | 6                                       | 3                       | 23        | 32    |
| Per cent of cases treated  | 100          | 3.17                                    | 1.58                    | 12.16     | 16.9  |

\*Includes one carcinoma of cervix following supravaginal hysterectomy.

The incidence, 16.9 per cent, of intestinal irradiation injuries which occurred in patients treated in our cancer clinic appears to be relatively high. This is true because in this series, every case of proved injury has been reported regardless of the fact that some were extremely mild, giving rise to only transient symptoms. In previously published reports, statistical data have included only the severe types of injuries requiring active treatment or surgical intervention for relief of symptoms. Had it not been our policy to investigate all cases with postirradiation intestinal symptoms, some of the injuries reported in this series would undoubtedly have been missed.

TABLE II. SUMMARY OF DIAGNOSES AND DISTRIBUTION OF THE 38 CASES AS TO CELL TYPE (EWING)

| DIAGNOSIS                | NO. OF CASES | CELL TYPE (EWING) |     |    |     |   |   |
|--------------------------|--------------|-------------------|-----|----|-----|---|---|
|                          |              | 1                 | 1-2 | 2  | 2-3 | 3 | 4 |
| Adenocarcinoma:          |              |                   |     |    |     |   |   |
| Corpus                   | 1            |                   |     |    |     | 1 |   |
| Cervix                   | 4            |                   |     | 1  |     | 3 |   |
| Squamous cell Carcinoma: |              |                   |     |    |     |   |   |
| Cervix                   | 33           | 2                 | 5   | 22 | 1   | 2 | 1 |
| Total                    | 38           | 2                 | 5   | 23 | 1   | 6 | 1 |





A.



B.

Fig. 3.—Mrs. J. (Hospital No. 68812), aged 51 years, was treated for squamous cell carcinoma of cervix with 4,800 mg. hr. of radium delivered in forty-eight hours and 8,800 r. of roentgen therapy in twenty-nine days. Intestinal symptoms began at four and one-half months after termination of irradiation. Diagnosis of intestinal stricture, A, was made one month later. Treatment was palliative. At two years and seven months after the diagnosis of intestinal stricture was made, the patient is free of intestinal symptoms, and roentgen study, B, shows the bowel to be practically normal in appearance. *Comment:* This is a good demonstration of Nature's success in healing such injuries.

Acute proctosigmoiditis is the mildest form of intestinal injury observed as a result of the secondary effects of irradiation therapy for uterine carcinoma. Characteristic intestinal symptoms appearing during the course of treatment or soon after its completion give the first warning of the presence of such an injury. The symptoms include abdominal pain, diarrhea, rectal tenesmus, and the passage of small amounts of blood and mucus by rectum.



A.



B.

Fig. 2.—Mrs. E. (Hospital No. 75463), aged 59 years, was treated for adenocarcinoma of cervix with 4,200 mg. hr. of radium delivered in twenty-four hours and 8,000 r. of roentgen therapy in thirty-six days. Onset of symptoms and diagnosis of intestinal stricture, A, occurred at five months after irradiation. Patient was free of symptoms and roentgen examination, B, made thirty-nine days after Fig. 2, A showed much less constriction of the bowel at the site of injury. Sigmoidoscopic examination showed an increase in the size of the bowel lumen. *Comment:* Rapid improvement would suggest that hyperemia, edema, and spasm of the bowel were important factors in causation of the stricture seen in A.

Examination will reveal a typical localized inflammatory process involving the anterior wall of the rectum and distal end of the sigmoid

at about the level of the cervix. The mucous membrane over the area is soft to palpation, intensely hyperemic in appearance or edematous with considerable mucous secretion over its surface. Trauma of the palpating finger or passage of a proctoscope readily induces slight bleeding. With a bland diet and suitable palliative treatment these mild injuries heal spontaneously and symptoms disappear soon after termination of irradiation therapy leaving no evidence of damage to the mucosa or wall of the intestine.

When injury to the bowel is more severe than that which causes an acute proctitis, ulceration of the intestine usually occurs. Although ulcerative lesions have been observed in both the rectum and sigmoid, the usual location for their development is on the anterior wall of the bowel at about the level of the cervix or at about 8 to 10 cm. from the anus.

Rectal examination will reveal an ulcer at least 1 to 2 cm. in diameter with a grayish white slough over its surface and an area of intense hyperemia and edema about its margin. Trauma of examination or evacuation of bowel contents readily induces bleeding. The extent of ulcerative lesions probably depends not only upon the severity of the original injuries but also upon secondary infection of the injured areas. In a small percentage of these cases, perforation of the bowel occurs into the peritoneal cavity, causing peritonitis; into the vagina, producing rectovaginal fistulas; or into the perirectal tissues, giving rise to ischiorectal abscesses requiring incision and drainage.

Ulcerative lesions make their appearance at any time from soon after termination of irradiation therapy to within several weeks or months later. They tend to heal slowly with separation of sloughs from their bases and inward growth of the surrounding healthy intestinal mucosa. When healing is complete the mucosa is pale and atrophic in appearance with some evidence of telangiectasis. Palpation of the lesion is likely to reveal some fixation as a result of the formation of fibrous tissue beneath the injured area. In some cases this increase in fibrous tissue extends into the wall of the intestine, constricting its lumen. Symptoms of a partial or complete organic obstruction may then appear.

At the onset, symptoms caused by intestinal irradiation ulcers may be the same as those resulting from irradiation proctitis but are likely to be more severe. In many of the cases in our series, the initial symptoms were those of partial intestinal obstruction due to a reduction in size of the bowel lumen as a result of hyperemia, edema and spasm of the intestinal wall at the site of an ulcerative lesion.

Injuries resulting in acute proctitis and ulcerative lesions appear to be confined essentially to the mucosa and wall of the intestine itself and have been referred to as "intrinsic lesions."<sup>2</sup> There are a few other cases in which the primary injury appears to have involved the perirectal tissues. The characteristic tissue reaction following such injuries is the formation of a diffuse mass of fibrous tissue involving all the



A.



B.



C.

Fig. 4.—Mrs. M. (Hospital No. 60323), aged 56 years, was treated for adenocarcinoma of cervix with 4,800 mg. hr. of radium in thirty-six hours, and 8,800 r. of roentgen therapy in thirty-two days. Intestinal symptoms began two months after termination of irradiation therapy. Diagnosis of intestinal stricture, A, was made as soon as symptoms appeared. At four months after irradiation, symptoms were less troublesome although a roentgenogram, B, still showed definite constriction of the bowel at the site of the injury. Another roentgenogram, C, made four years after irradiation shows less constriction of the bowel. At this time the patient was symptom free, and has continued in good health up to now, over six years from time of irradiation therapy. Comment: This shows the success of palliative therapy and that bowel function may be normal although evidence of stricture persists.

called "frozen pelvis" caused by massive invasion of all pelvic structures by malignancy. It may be associated with an ulcerative lesion of the bowel. As healing of this type of injury progresses, the lower bowel is likely to be distorted by contraction of the fibrous tissue and by external pressure causing intestinal obstruction.

Roentgen studies of the bowel are essential for diagnosis and proper management of many intestinal irradiation injuries. Some injuries resulting in strictures of the bowel occur at levels which do not permit satisfactory examinations through a sigmoidoscope. In others narrowing of the bowel lumen at the site of an injury prevents passage of a



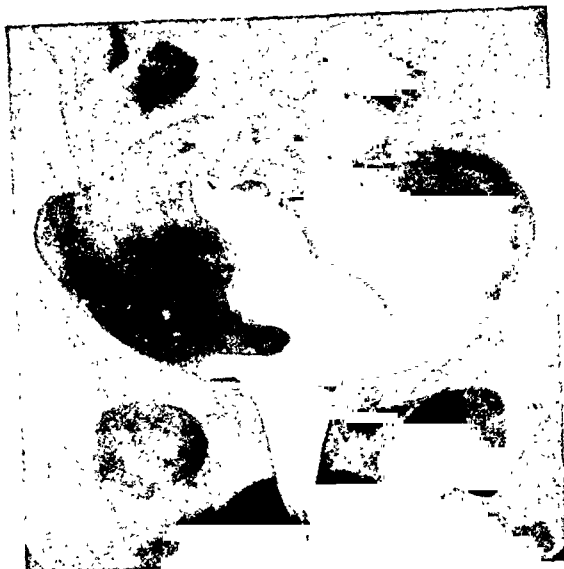
Fig. 6.—Mrs. T. (Hospital No. 70965), aged 63 years, was treated for squamous cell carcinoma of cervix with 6,000 mg. hr. of radium delivered in forty-eight hours, and roentgen therapy 8,400 r. in thirty-eight days. Onset of symptoms and diagnosis of intestinal stricture, occurred at two months after termination of irradiation therapy. Pelvic examination at operation, one week after diagnosis was made, showed the sigmoid markedly thickened for a distance of 10 cm. and adherent to the uterus. A loop of ileum was fixed by adhesions to the peritoneum of the cul-de-sac and was thickened for a distance of 12 cm. Its lumen was slightly constricted. Nonviable cancer cells were found in tissue removed from the surface of the ileum at its point of attachment in the cul-de-sac. The surgical procedure adopted was . . . . . This patient died three months after operation from generalized . . . . . This case shows the risk of bowel injury to adherent loop . . . . . of bowel stricture caused by irradiation was confirmed by operative findings. Operation was necessary one week after patient came under observation for bowel symptoms.

sigmoidoscope to a point at which the lesion can be satisfactorily visualized. By roentgen studies the existence and location of intestinal strictures can be determined and the success of palliative therapy can be checked. The decision as to whether palliative therapy should be continued or surgical intervention is necessary is usually based on physical symptoms and the results of such studies.

Figs. 1 to 8 show typical roentgen findings in some of the cases included in this series.

All of the 38 cases in the series that developed intestinal irradiation injuries had treatment with radium, and 27 of the 38 cases had additional roentgen therapy. In 19 of the cases, radium treatment was given

pelvic structures below the uterocervical junction and extending upward and backward to the second or third sacral vertebra. This type of tissue reaction to irradiation referred to as an "extrinsic lesion"<sup>2</sup> produces a pelvic condition which is difficult to differentiate from the so-



A.



B.

Fig. 5.—Mrs. M. (Hospital No. 74794), aged 52 years, was treated for squamous cell carcinoma of cervix with 4,200 mg. hr. of radium delivered in twenty-four hours, and 8,000 r. of roentgen therapy in fifty-one days. Intestinal symptoms began immediately following irradiation and the diagnosis of intestinal stricture, A, was made at three months from termination of irradiation. Pelvic examination showed a "frozen pelvis" from the so-called "extrinsic" type of injury. This is probably responsible for the distorted appearance of the lower bowel. A roentgenogram, B, made seven months later shows considerable improvement in the strictured bowel. At one year and nine months from the time the diagnosis was made the patient still has intestinal symptoms but is much improved. Comment: This is a good example of disturbance in bowel function from an "extrinsic" irradiation injury which has been treated by palliative means.

in one application and in the remaining 19 cases two applications were used. Roentgen therapy preceded treatment with radium in only one case.

Table V is a summary of the irradiation treatment and outcome of 9 cases in which intestinal injuries occurred without evidence of subsequent stricture. In 6 of the 9 cases, a diagnosis of proctosigmoiditis was made, and in 3 cases ulceration of the bowel also occurred at the site of the injury. In one case the ulcer perforated the rectovaginal septum, causing a rectovaginal fistula which healed spontaneously after two months. It will be noted in Table V that:

1. Onset of intestinal symptoms was from immediately following radium therapy in 5 cases to one year in one of the ulcer cases.
2. Diagnosis of an intestinal lesion was made in from one week to fourteen months after irradiation therapy.
3. Healing of the intestinal injuries was spontaneous in all of the 9 cases including the one with rectovaginal fistula and the two that died. At time of death these two patients had no intestinal symptoms.

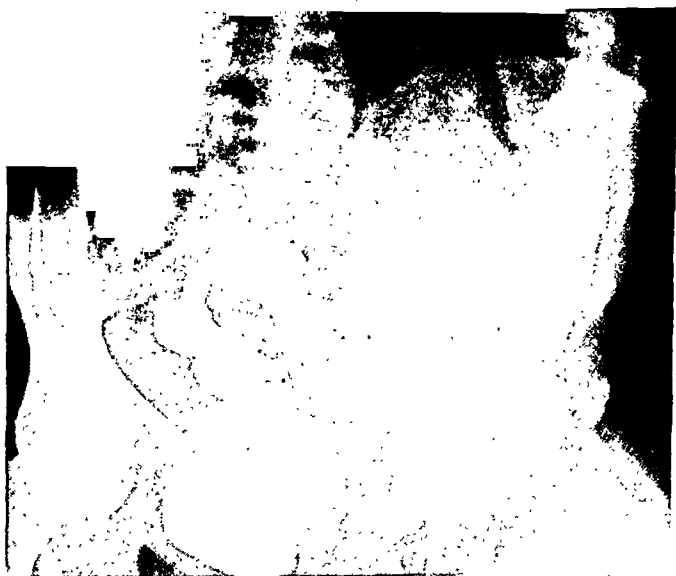


Fig. 8.—Mrs. L. (Hospital No. 55947), aged 45 years, was treated for squamous cell carcinoma of cervix with 6,000 mg. hr. of radium in forty-eight hours. No roentgen therapy was used. Intestinal symptoms began at three months after irradiation therapy, but a diagnosis of intestinal stricture was not made until five and one-half years after she was treated. This patient was operated upon eight months after the diagnosis of intestinal stricture was made. At operation the mid-portion of the sigmoid was found adherent to the uterus and left uterine adnexa. The wall of the sigmoid was thickened for a distance of 10 cm. It was inflamed, necrotic, and perforated at the point of its attachment to the uterus. The operative procedure was resection of the damaged portion of the sigmoid by the Gibson-Bal-four technique, and colostomy. This patient died one year and five months after operation from generalized carcinomatosis. *Comment:* The possibility of the development of intestinal obstruction from an irradiation injury at any time following treatment of uterine carcinoma must always be kept in mind.

In the series of 38 cases of irradiation injuries, 29 had intestinal strictures as proved by roentgen studies of the injured bowel. In 18 of the 29 cases with strictures, symptoms have been relieved or controlled by palliative means. The results of treatment of these cases are summarized in Table VI.



A.



B.

Fig. 7.—Mrs. W. (Hospital No. 74210), aged 40 years, was treated for squamous cell carcinoma of cervix with 4,200 mg. hr. of radium delivered in twenty-four hours, and 7,600 r. of roentgen therapy in thirty-six days. Intestinal symptoms began immediately following irradiation and intestinal stricture, A, was diagnosed at six months after termination of irradiation. Palliative treatment failed and a diagnosis of complete intestinal obstruction, B, was made five months later. At operation no evidence of malignancy was found in the abdomen or pelvis. The wall of the rectosigmoid was markedly thickened for a distance of 10 cm. extending down to the floor of the cul-de-sac. The wall of the bowel was ulcerated and necrotic, and an impending perforation was sealed off by an adherent loop of ileum. The operative procedure adopted was permanent colostomy and abdominoperineal resection, removing the rectum and the damaged portion of the sigmoid. This patient is alive and well at seven months after operation. *Comment:* Timely operative interference is a life-saving measure for some patients who develop postirradiation intestinal injuries.



From Table VI, it will be noted that in from three months to over six years of observation, 13 of the 18 patients had become symptom free, 2 were improved, 1 was unimproved, and 3 died of generalized carcinomatosis.

It is frequently difficult to differentiate between intestinal obstruction caused by tissue reaction to irradiation injury and conditions resulting from malignancy. The diagnosis of an irradiation intestinal stricture in any patient under observation is based upon improvement in general health following treatment, relief of intestinal symptoms following palliative treatment and roentgen evidence of increasing size of the lumen of the bowel at the site of injury.

Table VII is a summary of facts regarding irradiation therapy and diagnosis in 11 of the 29 cases of intestinal stricture which required surgical intervention for relief of symptoms. In this table it will be noted that:

1. Diagnosis of stricture requiring operation was made in from two months to five years and five months after termination of irradiation therapy.
2. Location of the stricture was in the rectum in one case, in the sigmoid in six cases, in the rectosigmoid in three cases and in the ileum in one case. In one case of sigmoid injury the ileum was also involved.

Table VIII is a summary of the surgical techniques used and outcome of the 11 cases of intestinal stricture that were operated upon for relief of symptoms.

Surgical indications which arise in the treatment of these cases include procedures to:

1. Relieve pain, bleeding and partial or complete intestinal obstruction.
2. Remove necrotic bowel which may perforate resulting in death from peritonitis.
3. Promote healing of ulcerative lesions by diverting the fecal stream. In some cases this can be accomplished by colostomy which can be closed after the intestinal injury has healed.

Success in the treatment of irradiation intestinal injuries requires the skill and judgment of an experienced surgeon. He must have the ability to select the surgical procedure best suited for treatment of injuries which vary considerably as to their extent and location.

Surgical treatment of such injuries is not infrequently complicated by the fact that they occur in patients who are either poor surgical risks or are in poor physical condition when operative interference becomes necessary.

Another factor which must be taken into consideration is the disturbance in circulation which occurs in tissues which have been subjected to intensive irradiation. With this in mind colostomy may be the primary procedure of choice to avoid complications arising from failure of wound healing following intestinal resection and anastomosis.

TABLE III A. SUMMARY OF RADIUM DOSAGE USED IN 19 CASES WITH INTESTINAL INJURIES FOLLOWING ONE APPLICATION OF RADIUM FOR CARCINOMA OF THE UTERUS

*Carcinoma of Corpus Uteri*, 1 Case. Radium dosage in the one case was 2,400 mg. hr. given in one application to the uterine cavity in 24 hours.

*Carcinoma of Cervix Uteri*, 18 Cases. In the 18 cases one application of radium was used as follows:

| LOCATION OF APPLICATORS      | DOSE IN MILLIGRAM HOURS |                    |                    |                           | CASES TREATED |
|------------------------------|-------------------------|--------------------|--------------------|---------------------------|---------------|
|                              | 2,000 IN<br>24 HR.      | 2,400 IN<br>24 HR. | 3,000 IN<br>30 HR. | 600-1,800<br>IN<br>24 HR. |               |
| Cervical canal               | 1                       | 16                 | 1                  |                           | 18            |
| Cervix (vaginal surface)     |                         | 1                  |                    |                           | 1             |
| Parametrium (radium needles) |                         |                    |                    | 18                        | 18            |

Range of total dosage in the 18 cases was from 3,000 to 4,500 mg. hr. in 17 cases and 6,000 mg. hr. in one case.

17 of the 19 cases in this group had additional *roentgen therapy* ranging from 7,600 to 10,000 r. within 26 to 51 days.

TABLE III B. SUMMARY OF RADIUM DOSAGE USED IN 19 CASES WITH INTESTINAL INJURIES FOLLOWING TWO APPLICATIONS OF RADIUM FOR CARCINOMA OF THE CERVIX UTERI

| LOCATION OF APPLICATORS            | FIRST APPLICATION       |                    |                              | SECOND APPLICATION      |                    |                    |                                |
|------------------------------------|-------------------------|--------------------|------------------------------|-------------------------|--------------------|--------------------|--------------------------------|
|                                    | DOSE IN MILLIGRAM HOURS |                    |                              | DOSE IN MILLIGRAM HOURS |                    |                    |                                |
|                                    | 1,200 IN<br>24 HR.      | 2,400 IN<br>24 HR. | 600 TO<br>1,800 IN<br>24 HR. | 1,500 IN<br>15 HR.      | 1,200 IN<br>24 HR. | 2,400 IN<br>24 HR. | 1,500 TO<br>1,800 IN<br>24 HR. |
| Cervical canal                     |                         | 18                 |                              | 1                       |                    | 2                  |                                |
| Cervix and uterine cavity          | 1                       |                    |                              |                         |                    |                    |                                |
| Parametria (radium needles)        |                         |                    | 18                           |                         | 1                  |                    |                                |
| Vaginal fornices (Clark colpostat) |                         |                    |                              |                         |                    |                    | 16                             |

Range of total dosage in the 19 cases was from 4,800 to 6,000 milligram hours. Total duration of radium exposure was 39 hours in one case and 48 hours in 18 cases.

10 cases in this group had *roentgen therapy* ranging from 6,000 to 10,000 r. within 22 to 50 days.

TABLE IV. SUMMARY OF WOMAN'S HOSPITAL ROENTGEN THERAPY TECHNIQUE USED IN CASES OF CARCINOMA OF CERVIX UTERI

|   |                       |
|---|-----------------------|
| Voltage: 200,000 (peak)   | Distance: 70 cm.      |
| Filtration:   | Intensity:            |
| (a) .75 mm. copper. 2 mm. aluminum.   | (a) 25 r. per minute. |
| (b) .4 mm. tin. .25 mm. copper.   | (b) 10 r. per minute. |
| 1.0 mm. aluminum.   |                       |
| Number of fields: 4-6.  |                       |
| Size of fields: Maximum 16 x 12 cm.; average 16 x 10 cm.  |                       |
| Centering of fields: Over parametria with protection of an area along the mid-line—2 to 3 cm. in width. |                       |
| Daily dose: 150-200 r. to each of two fields.   |                       |
| 150 r. per field routinely since 1938.  |                       |
| Total amount administered to pelvis (measured in air): 8,000-10,000 r.                                  |                       |
| Duration of cycle: 23 to 42 days (present minimum 30 days).   |                       |

TABLE VI. SUMMARY OF DATA REGARDING 18 CASES WITH INTESTINAL IRRADIATION STRICTURES IN WHICH RELIEF OF SYMPTOMS FOLLOWED PALIATIVE TREATMENT

| AGE | STAGE OF DISEASE  |         | IRRADIATION   |          |          |           | TIME. END OF IRRAD. TO ROENT. |                    |     | TIME. DIAGNOSIS OF STRICTURE TO PRESENT AND PRESENT CONDITION |   |               |                   |   |
|-----|-------------------|---------|---------------|----------|----------|-----------|-------------------------------|--------------------|-----|---|---|---------------|-------------------|---|
|     |                   |         | RADIUM        |          | ROENTGEN |           | YR.                           | DIAG. OF STRICTURE |     | TIME  |   | SYMP-TOM FREE | OUTCOME OF OTHERS |   |
|     |                   |         | DOSE MG. IIR. | TIME HR. | DOSE R.  | TIME DAYS |                               | MO.                | YR. | MO.   |   |               |                   |   |
|     | LEAGUE OF NATIONS | SCHMITZ |               |          |          |           |                               |                    |     |   |   |               |                   |   |
| 50  | 1                 | 2       | 3,000         | 33       | 8,000    | 33        | 1                             | 6                  | 2   | 6   | 2 | 6             | x                 | Improved. Bowel less con-stricted   |
| 50  | 2                 | 3       | 3,600         | 34       | 8,400    | 34        | 5                             |                    | 1   | 4   | 1 | 4             | x                 |   |
| 33  | 2                 | 3       | 4,200         | 24       | 8,000    | 26        |                               | 6                  | 2   | 1   | 2 | 1             | x                 |   |
| 52  | 2                 | 3       | 4,200         | 24       | 8,000    | 51        |                               | 4                  |     |   |   | 9             |                   |   |
| 35  | 2                 | 3       | 4,200         | 24       | None     | -         |                               |                    | 1   | 10  | 1 | 2             |                   | Unimproved. Symptoms per-sist   |
| 40  | 1                 | 2       | 4,200         | 24       | 8,000    | 24        |                               | 4                  | 4   |   | 4 | 2             | x                 | Dead. 1 yr. 5 mo.<br>Carcinoma metastasis   |
| 59  | 1                 | 2       | 4,200         | 24       | 8,000    | 36        |                               | 5                  |     |   |   | 3             | x                 |   |
| 32  | 2                 | 3       | 4,200         | 24       | 8,000    | 40        |                               | 5                  | -   |   | - | -             | x                 |   |
| 38  | 2                 | 3       | 4,200         | 24       | 10,000   | 35        |                               | 5                  |     |   |   | 8             | x                 |   |
| 51  | 1                 | 2       | 4,800         | 48       | 8,800    | 29        |                               | 5                  | 2   |   | 2 | 5             | x                 | Improved. Bowel less con-stricted   |
| 56  | 1                 | 1       | 4,800         | 36       | 8,800    | 32        |                               | 2                  | 6   |   | 6 | 3             | x                 |   |
| 63  | 3                 | 3       | 6,000         | 48       | 10,000   | 35        |                               | 6                  | 3   | 15  | 3 | 1             |                   |   |
| 44  | 2                 | 3       | 6,000         | 48       | 8,800    | 31        |                               | 5                  | 2   | 15  | 2 | 3             | x                 |   |
| 44  | 2                 | 3       | 6,000         | 48       | 8,000    | 28        |                               | 3                  | 2   |   | 2 | 6             | x                 | Dead. 1 yr. 10 mo.<br>Carcinoma metastasis<br>Dead. 2 yr. 3 mo.<br>Carcinoma metastasis |
| 50  | 1                 | 2       | 6,000         | 48       | 6,000    | 22        | 2                             | 5                  | 2   |   | 2 | -             | x                 |   |
| 38  | 1                 | 2       | 6,000         | 48       | None     | -         |                               |                    | -   |   | - | -             | x                 |   |
| 43  | 1                 | 2       | 6,000         | 48       | None     | -         |                               | 1                  | -   |   | - | -             | x                 |   |
| 35  | 2                 | 3       | 6,000         | 48       | 7,700    | 33        |                               | 9                  |     |   |   |               | x                 |   |

Improved. Bowel less con-  
stricted

Unimproved. Symptoms per-  
sist

Dead. 1 yr. 5 mo.  
Carcinoma metastasis

Improved. Bowel less con-  
stricted

Dead. 1 yr. 10 mo.  
Carcinoma metastasis

Dead. 2 yr. 3 mo.  
Carcinoma metastasis

TABLE V. SUMMARY OF DATA REGARDING 9 CASES WITH INTESTINAL INJURY WITHOUT EVIDENCE OF STRICTURE

| DIAGNOSIS          | CASE | AGE | STAGE OF DISEASE   |         | IRRADIATION   |           |              |                 | TIME FROM TERMINATION OF IRRADIATION TO: |     |     | TIME FROM DIAGNOSIS TO PRESENT |     | PRESENT CONDITION                           |
|--------------------|------|-----|--------------------|---------|---------------|-----------|--------------|-----------------|--|-----|-----|--------------------------------|-----|---|
|                    |      |     |                    |         | RADIUM        |           | ROENTGEN RAY |                 |  |     |     |                                |     |   |
|                    |      |     | LEAGUE OF NA-TIONS | SCHMITZ | DOSE MG. IIR. | TIME IIR. | DOSE R.      | TREAT-MENT DAYS | ONSET OF SYMPTOMS                        | MO. | WK. | YR.                            | MO. |   |
|                    |      |     |                    |         |               |           |              |                 |  |     |     |                                |     |   |
| Proctosig-moiditis | 1    | 51  | -                  | -       | 2,400         | 24        | 7,800        | 26              | Immediate                                | 1   | 1   | 2                              | 2   | Symptom free                                |
|                    | 2    | 54  | 2                  | 3       | 3,500         | 20        | 3,200        | 10              | Immediate                                | 1   | 1   | 4                              | 8   | Symptom free                                |
|                    | 3    | 52  | 1                  | 2       | 3,600         | 24        | 8,000        | 40              | Immediate                                | 10  | 1   | -                              | 7   | Symptom free                                |
|                    | 4    | 57  | 2                  | 3       | 6,000         | 24        | None         | -               | Immediate                                |     |     | -                              | -   | Dead. Cardiovascular dis-ease after 4 years |
|                    | 5    | 46  | 2                  | 3       | 6,000         | 48        | 7,200        | 29              | Immediate                                |     |     | -                              | -   | Dead. Carcinoma metas-tasis after 1 year    |
|                    | 6    | 30  | 2                  | 3       | 6,000         | 48        | 8,000        | 50              | Immediate                                | 3   | 2   | 4                              | 7   | Symptom free                                |
| Ulcer              | 7    | 41  | 1                  | 2       | 4,200         | 24        | 8,400        | 33              | Immediate                                |     | 1   | 1                              | 4   | Symptom free                                |
|                    | 8    | 58  | 2                  | 3       | 4,500         | 30        | 10,000       | 32              | 12 mo.                                   | 14  |     | 3                              | 10  | Symptom free                                |
|                    | 9    | 66  | 2                  | 3       | 5,400         | 48        | 8,000        | 23              | 6 mo. R. V. fistula                      | 6   |     | 2                              | 5   | Rectovaginal fistula healed after 2 months  |

Dignosis: Case 1, carcinoma corpus uteri, all others carcinoma cervix uteri.

In Case 2, roentgen therapy was discontinued on account of intestinal symptoms.

In Cases 1, 2, 3, 5, and 7, intestinal symptoms began immediately after radium.

TABLE VIII. SUMMARY OF FINDINGS, SURGICAL TECHNIQUES EMPLOYED AND OUTCOME OF 11 CASES OPERATED UPON FOR INTESTINAL STRICTURES

| LOCATION OF STRICTURE | OPERATION  | POSTOPERATIVE FOLLOW-UP |                      |     |      |                              |  |
|-----------------------|--|-------------------------|----------------------|-----|------|------------------------------|--|
|                       |  | ALIVE AND WELL          | TIME SINCE OPERATION |     | DIED | TIME FROM OPERATION TO DEATH | CAUSE OF DEATH   |
|                       |  |                         | YR.                  | MO. |      |                              |  |
| Sigmoid               | Partial resection sigmoid (Gibson-Balfour)               | +                       | 3                    | 10  |      |                              |  |
| Sigmoid               | Partial resection sigmoid (Gibson-Balfour)               | +                       | 3                    | 7   |      |                              |  |
| Sigmoid               | Partial resection sigmoid. Colostomy                     |                         |                      |     | +    | 17 months                    | Generalized carcinomatosis                                       |
| Recto-sigmoid         | Abdominoperineal resection sigmoid and rectum. Colostomy | +                       |                      | 7   |      |                              |  |
| Ileum                 | Resection of 25 cm. ileum                                |                         |                      |     | +    | 4 days                       | Peritonitis  |
| Sigmoid               | Colostomy (Mikulicz)                                     |                         |                      |     | +    | 3 days                       | Peritonitis  |
| Recto-sigmoid         | Colostomy (Mikulicz)                                     | +                       | 2                    | 1   |      |                              |  |
| Sigmoid               | Colostomy (Mikulicz)                                     |                         |                      |     | +    | 5 weeks                      | Intestinal hemorrhage  |
| Sigmoid               | Colostomy (Mikulicz)                                     |                         |                      |     | +    | 3 months                     | Generalized carcinomatosis                                       |
| Ileum                 | Adherent ileum Released                                  |                         |                      |     |      |                              |  |
| Rectum                | Colostomy (Devine)                                       |                         |                      |     | +    | 3 months                     | Intestinal hemorrhage  |
| Sigmoid               | Cecostomy  |                         |                      |     | +    | 46 days                      | Necrosis of sigmoid. Small bowel obstruction. Pneumonia. Autopsy |

In cases in which intestinal injuries have occurred as a result of irradiation treatments for uterine carcinoma, it is often impossible to determine whether they have been caused by radium or roentgen ray therapy. However, it is generally agreed that they are invariably due to overdosage of irradiation and that the primary injury is to the blood vessels which supply the injured bowel.<sup>2</sup> It is believed that damage to some of the smaller branches of the hemorrhoidal vessels results in their becoming thrombosed and occluded. This leads to infarction and mucosal ulceration in the portion of the bowel from which the blood supply has been withdrawn. There is reason to believe that muscular spasm of the bowel wall at the site of the injury may be another factor in decreasing its blood supply.



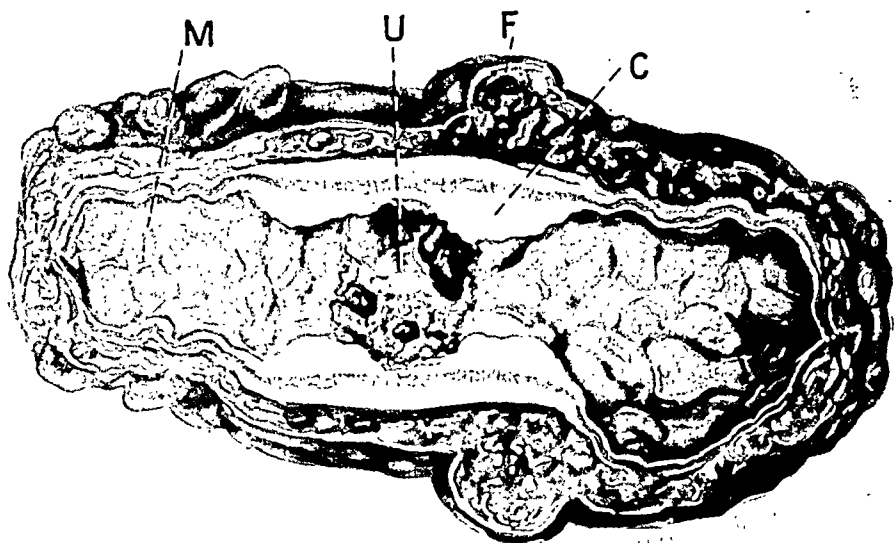


Fig. 10.—Showing a longitudinal section of this same specimen of bowel. The peritoneum and subperitoneal tissues, *F*, are markedly edematous. A typical mucosal ulcer, *U*, can be seen. Induration of the wall extends far beyond the limits of the ulcer. Nature's attempt to heal the injury has resulted in a marked formation of fibrous tissue, *C*, which has narrowed the lumen of the bowel.

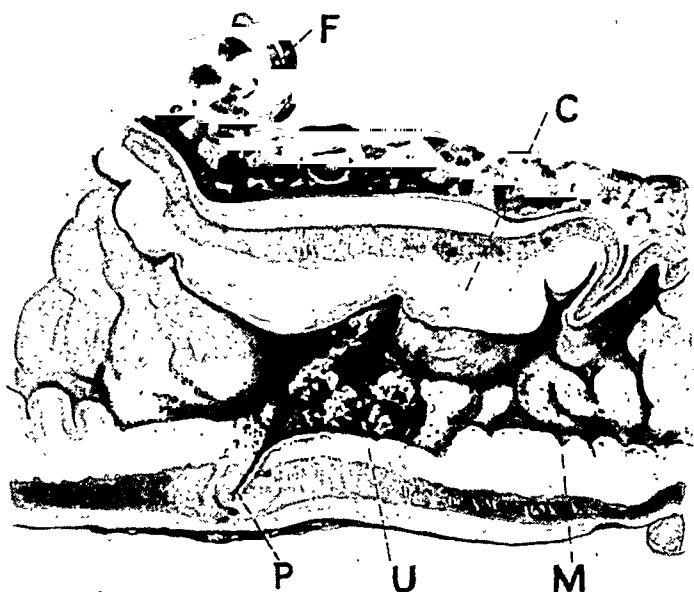


Fig. 11.—Longitudinal section of the same specimen but in a different plane. This shows the same characteristic anatomic changes seen in Fig. 10. In addition it has been made at a point at which the mucosal ulcer, *U*, has nearly perforated the intestinal wall at *P*.

From the study of specimens in our own laboratory, it appears that the blood supply to the injured bowel is gradually rather than suddenly withdrawn. The basis for this conclusion is that within the areas of tissue necrosis observed, foci of reparative (inflammatory) tissue reaction can be identified. It is assumed that the cellular elements for this defensive tissue reaction must have been supplied by blood vessels which had not lost their function.

Figs. 9, 10, and 11 are drawings made from fresh surgical specimens.

A reduction in the incidence of these serious intestinal complications of irradiation therapy for uterine carcinoma must depend upon a better understanding of their etiology, recognition of the fact that they may make their appearance at any time from immediately following irradiation therapy to within several years thereafter, and elimination of conditions which are known to predispose to their occurrence.

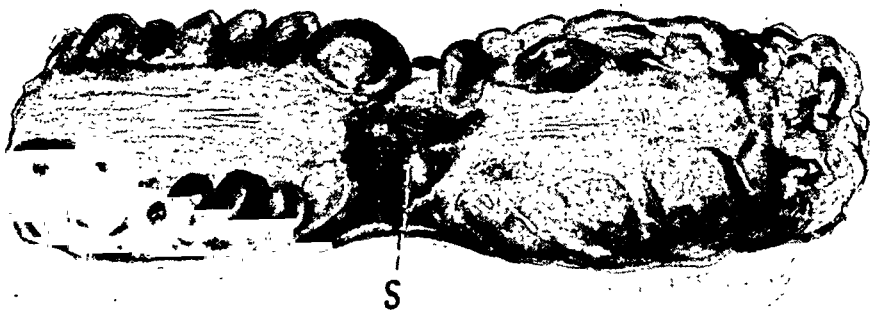


Fig. 9.—Showing the characteristic external appearance of the bowel which has been injured by irradiation. The wall is thickened and has the consistency of a thick-walled "rubber tube." In the midportion of this specimen, there is a constricted, necrotic area, *S*. The dark color is due to extravasation of blood beneath the peritoneum.

Both clinical and experimental studies have contributed to our knowledge of factors which may be responsible for such injuries. The unusual susceptibility of the intestinal mucosa to damage from irradiation has been well established.<sup>1</sup> Overdosage of irradiation, which may be a frequent cause of such injuries, is undoubtedly the result of faulty technique or of conditions which are difficult to control. Cases have been reported in which intestinal injuries were due to accidental dislodgement of radium applicators from the cervical canal or uterine cavity to the vagina.

Other conditions which may result in excessive exposure of the intestine to radium include: a retroverted uterus, a uterus with a thin muscular wall and peritoneal adhesions which fix one or more loops of the intestine to the external surface of the uterus, or to the cervical stump following supravaginal hysterectomy. Furthermore, Todd has called attention to the fact that "the question of overdosage is a rela-



5. Success in the treatment of intestinal irradiation injuries will depend upon a knowledge of the possibility of their occurrence, early diagnosis, suitable palliative treatment and, when indicated, timely operative interference.

I wish to acknowledge my indebtedness to Dr. William Crawford White, Consultant in Surgery, Dr. John E. Hutton, Gastroenterologist, and Dr. Harriett McIntosh, Roentgenologist, all of the Woman's Hospital, for their kind assistance in the diagnosis and treatment of the cases that have been reported. Their enthusiasm has done much to arouse the interest of our staff in this important subject.

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#### DISCUSSION

DR. JOE V. MEIGS, BOSTON, MASS. (by invitation).—There is apparently an increase in the number of bowel injuries following treatment of cervical cancer with x-ray and radium. It is possible in the past that such patients, treated with radium alone, went to other clinics and were not recorded, while others have had tenesmus, pain, and diarrhea but have recovered without treatment. It is more likely that the addition of roentgen therapy to the usual radium treatment has been an equal contributor to bowel stricture. Before the advent of deep roentgen therapy, an occasional case of obstruction was seen but recently more patients have come with serious lesions.

At the Massachusetts General Hospital and the Pondville Hospital we have had 30 such patients, or 3.6 per cent out of a total of 800 who were given x-ray treatment plus radium. In four other cases strictures followed radium alone. A great many other patients with symptoms of bleeding, tenesmus, pain, etc., were seen but are not reported here as this discussion deals only with actual bowel strictures as demonstrated by proctoscopy, x-ray, or operation.

The mortality following the treatment of the obstruction is low, nevertheless radiation stricture is a trying and difficult complication. About 100 of our 800 cases had supervoltage or 1,000—1,200 kv. therapy. Of these 100, 8 patients developed obstructing lesions. Twenty of the total of 30 followed 200 kv. therapy and 2 followed 400 kv. treatment. It is very probable that more cases will follow the million volt therapy until the proper dosage has been learned from a large experience.

Of the 34 patients with obstruction and stricture at the Massachusetts General Hospital and Pondville Hospital, 22 were operated upon. In the 12 patients not operated upon and diagnosed by x-ray and proctoscopy, 6 had lesions in the rectum and 6 in the sigmoid. The symptoms in all cases consisted of pain, rectal bleeding, nausea, vomiting, distention, and tenesmus. Of those operated upon, 11 had a colostomy done; 1 a colostomy with posterior excision of the rectum; 2 had ileo-transverse colostomies plus resection of the ileum with sigmoid colostomy; 2 had ileo-transverse colostomies plus resection of the ileum; 2 had ileostomies; 2 had resection of the ileum; in 1 a piece of adherent ileum was released; and in 1 an entero-enterostomy was done.

There was only 1 postoperative death, but of the 22 patients operated upon, 4 have since died. The average time to the onset of bowel symptoms from the time

tive one." In other words, tissue tolerance to irradiation may be reduced by poor general health and tissue changes resulting from degenerative diseases.

In some cases overdosage is undoubtedly due to the combined effects of radium and roentgen ray irradiation. Danger from this source can be reduced if roentgen exposure is carefully focused on the lateral pelvic structures and adjacent gland-bearing areas.

Numerous suggestions have been made to prevent irradiation intestinal injuries. They include:

1. Procedures to prevent accidental dislodgement of radium applicators from the cervical canal and uterine cavity.

2. Distention of the vagina with gauze and insertion of a rectal tube during application of radium with the purpose of increasing the distance between the radium and walls of the rectum and sigmoid.

3. Caution in the use of irradiation for treatment of patients who have had pelvic infections or previous abdominal or pelvic operations.

4. Frequent changes in position of a patient during radium treatment with the hope of dislodging intestinal loops which may be in close proximity to the uterus.

5. Roentgen studies of the intestine before placing radium in the cervical canal or uterine cavity to determine whether loops of intestine are fixed to the uterus or cervical stump by adhesions. Evidence produced by such studies is not always conclusive.

6. Preirradiation exploratory laparotomy to determine whether loops of intestine are adherent in positions that might subject them to too much irradiation. This seems a radical procedure and does not eliminate the possibility of intestinal adhesions re-forming immediately after the exploratory operation.

7. Reduction of intensity of irradiation by:

- a. Using smaller amounts of radium and increasing duration of exposures.

- b. Decreasing the size of the fields of roentgen ray exposures and the amounts of roentgen therapy per treatment.

#### CONCLUSIONS

1. Sufficient irradiation to effect a cure of uterine carcinoma cannot be applied without some damage to the intestinal tracts of a considerable percentage of patients treated.

2. The true incidence of such injuries cannot be determined without routine diagnostic studies of the intestinal tracts of all patients who develop significant postirradiation intestinal symptoms.

3. The development of intestinal symptoms and especially those of intestinal obstruction at any time from a few weeks to several years after irradiation for uterine carcinoma should always suggest the possibility of a post-irradiation intestinal injury.

4. Careful diagnostic studies will serve to differentiate intestinal irradiation injuries from reactivations or extensions of malignant growths and may be the means of saving lives.

deaths within a few days from peritonitis is noteworthy, as is the fact that in most instances the operative procedure chosen has served its purpose well.

Dr. Aldridge's analysis places the percentage of intestinal complications, mild and severe, at a somewhat higher level than has been previously reported. However, we believe that it is no higher than will be found in most clinics if careful study of present-day therapy is carried out.

I would like briefly to state our experience at the Roosevelt Hospital with a group of cancer of the cervix cases, which includes both service and private patients, particularly those of Dr. Howard C. Taylor. This is a small series viewed against the larger experience of others here, but it is of some interest at the moment in that the radiation technique is so nearly like that used by Dr. Aldridge and therefore the two series may well be compared as to resulting intestinal injuries.

From 1935 to 1941 we have treated 100 cases of cervix carcinoma. These patients have received in and about the cervix and lower uterine canal between 3,000 and 5,000 mg. hr. of radium element in capsules with 0.5 mm. platinum filtration, of which 3,000 to 3,500 mg. hr. have been in the cervical canal. In the majority of instances this radiation was accomplished in one application but in a small number (those receiving a total of 4,500 to 5,000 mg. hr.) 1,500 to 1,800 mg. hr. of the total amount were given as a second application at least six weeks later.

High-voltage therapy either followed or preceded this element radiation at a six to eight weeks' interval with a machine similar to that used by Dr. Aldridge and delivering 45 r. per minute. Daily doses of 220 to 360 r. to one part only have been given (averaging in most cases about 320 r.) A total x-ray dosage of 6,000 to 7,500 r. has been employed, spread over from twenty-eight to forty-two days. (This is 2,000 to 2,500 r. less than Dr. Aldridge states.)

In these 100 cases we have had 13 instances of major intestinal damage as compared to Dr. Aldridge's 12.16 per cent. Nine of these occurred in the large bowel and 4 in the small bowel. In the large bowel 6 showed varying degrees of stricture of the rectosigmoid, some with ulcerative bleeding, but none has required operation. The time of appearance of symptoms of these injuries varied from two months to one year. Three developed rectovaginal fistula, one of which healed spontaneously, the other two being in advanced cases.

In the small bowel, constricting lesions occurred in the 4 cases in five months, six months, six months, and eleven months, respectively, after the termination of therapy. Three required small gut resection and two of these are now alive and free of disease in their fourth year. One, a stump case, who had a loop of ileum adherent to the cervix, developed stricture six months after radiation, and died after resection from intestinal thrombosis.

We have compared this series of 100 cases with 62 others treated from 1931 to 1934, when we were using almost double the amount of radium therapy in two applications but only about one-half the amount of high voltage therapy. In this group there were only 2 rectovaginal fistulas and no small bowel injuries. Thus in our experience with 162 cases we have noted a greater incidence and a greater variety of intestinal injuries since we have stepped up the amount of high voltage therapy given. We believe that gut damage, except in the one stump case, has had little if any relationship to the amount of radium radiation used. In our series it is too early to say whether an increased salvage will compensate for this increased incidence of intestinal damage. As a step toward prevention of these injuries we hope to:

1. Be more conscious of bowel proximity and screen our radium more effectively when necessary;
2. To reduce our daily high voltage dosage and spread it out over a longer period of time.

of treatment was one month to twelve months in 17 cases, with an average of six months; in 13 cases, from one year to seven years, with an average of 3.4 years. In 4 cases the correct dates of onset were not known.

One patient with symptoms of obstruction and bleeding, with stricture observed by x-ray six months after radiation treatment, was completely relieved of symptoms and an x-ray of her colon was normal without treatment at one year. In 2 patients temporary left-sided colostomies were closed successfully.

The largest dose of x-ray therapy was 9,200 roentgen units with the 1,200 kv. machine, and the smallest dose was 1,200 roentgen units with the 200 kv. machine. The largest dose of radium was 6,086 millicurie hours and the smallest was 2,000 millicurie hours.

To avoid injury to the bowel the rays must be prevented from striking it. To accomplish this is difficult in patients that have not been operated upon, but much more difficult in those who may have an adherent loop of bowel.

Perhaps radiation treatment of early cervical cancer is not the best method and perhaps surgery should be more widely used for early cases. This would avoid the dangers of radium and x-ray. The latter combination could be used for more extensive cases where the acceptance of a 3.6 per cent morbidity might be considered insignificant when attempting to cure the disease. About one-half of our cases of bowel injury were in an early operable group, and operation in this group would have been safer than radiation therapy.

It is my feeling that the answer to the apparent increase of bowel injuries is radical surgery for cancer of the cervix in certain cases, the use of high Trendelenburg position plus air injection in others, the use of the full bladder, and possibly the avoidance of x-ray therapy in patients who have been previously operated upon. The Trendelenburg position during treatment has been suggested, but the slanting position necessary is not possible with our present million volt therapy apparatus. Ten of our 34 patients had been operated upon and may have had adherent bowel, in which case this method would not have worked.

Air injection of the abdomen has been suggested, but this would not help those with adherent bowel. Others have suggested injecting air into the rectum and filling the bladder with some solution. Schatzki has suggested persuading the patient to drink plenty of water and treating her when the bladder is full, thus displacing the ileum out of the pelvis and pushing the sigmoid to the left. This would be helpful as the sigmoid and the ileum are most frequently injured. The position of the sigmoid in the pelvis is obviously responsible for its injury, and when a patient lies on her back, the terminal ileum is usually the lowest loop of small intestine and is in the pelvis. If the sigmoid and the small intestine could be pushed aside and out of the pelvis, injuries would not occur, but it is difficult to be sure that they are out of the way during 21 to 30 successive x-ray treatments and 2 radium treatments.

DR. THOMAS C. PEIGHTAL, NEW YORK, N. Y.—Dr. Aldridge has established the incidence of intestinal injury following irradiation of the uterus for cancer in a much more accurate manner than has been done heretofore. His records are most complete, so that his figures must indicate accurately the possibility or probability of intestinal injury in any series treated after the manner of procedure at the Woman's Hospital.

Most papers to date have recorded only major gut complications. In addition to these, Dr. Aldridge has enumerated for us the number of lesser intestinal involvements and has indicated that the majority of these have cleared up spontaneously under symptomatic therapy. Another most instructive feature of this presentation is his study of 11 obstructive injuries and the surgical methods used in overcoming these major complications. That there were only two postoperative

## HORMONAL INFLUENCES UPON THE URETER\*

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THIS article deals with our observations on ureteral peristalsis during the various phases of pregnancy and the puerperium. In addition, we present further confirmatory data that the ureter is subject to hormonal influences which regulate its peristaltic behavior. Before presenting these observations on ureteral peristalsis, a brief summary of our foregoing work on the physiologic changes occurring in the urinary tract during pregnancy is necessary. A portion of this work has previously been presented to this Society.

For many years we have known that dilatation changes occur in the urinary tract during pregnancy, but it was not until the development of intravenous urography, made possible by the original work of Rowntree in 1923 and further elaborated by Swick and Binz in 1929, that we have been aware of its nearly constant occurrence. In our urographic study of 27 normal pregnant women throughout the succeeding months of gestation and the puerperium, the most constant change noted was a dilatation of the pelvis and calyces of one or both kidneys, a dilatation, tortuosity and kinking of one or both ureters, and a lateral displacement of these structures. In addition, there was an apparent atony of the ureteral musculature observed. Every patient showed some deviation from the normal, ranging from a slight dilatation to a marked degree of hydronephrosis and hydroureter. The right kidney and ureter were more affected than the left. The dilatation of the ureter always began at the pelvic brim, and in not one of the patients studied was there found a definite and significant dilatation of the pelvic portion of this structure. With the advance of pregnancy, the dilatation of the upper urinary tract gradually increased to the time of delivery, and following this event there was a rather rapid regression to the normal state, taking place as a rule in twenty-eight days. It is a well-known fact that the presence of frank infection greatly retards the normal involution process. In this urographic study, it was found that with advancing pregnancy and with progressive dilatation of the ureter, the excretion time of the kidney was markedly retarded, so that frequently a delay of thirty to forty-five minutes was necessary before a satisfactory film could be obtained.

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From our experience we would urge the following:

1. Operative treatment of all small bowel lesions as early as possible after diagnosis can be made. (In our cases x-ray did not demonstrate adequately the multiplicity or extent of these small bowel injuries.)

2. Conservative treatment of large bowel irritations, ulcers, and strictures, as many of the latter which seem at first quite tight may function adequately with patience and time.

3. Dr. Aldridge has pointed out how extremely difficult it is at times to determine whether persistent pain plus mild obstruction may be due to radiation injury or to spread of growth. In such cases if there is satisfactory local regression of the carcinoma and the patient's general condition is improving, we would urge abdominal exploration, as in the few instances in which we have followed this plan we have been repaid by finding a readily remedied benign pain-producing lesion, or very small metastases on the lateral pelvic walls which were not beyond the limit of satisfactory surgical removal. If extensive growth is found, further therapy can be carried out with a sound knowledge of its location and extent.

DR. GEORGE GRAY WARD, NEW YORK, N. Y.—These intestinal injuries are more common than is generally realized. Several years ago we showed that rectal injuries occurred in about 5 to 6 per cent of 688 cases treated and followed up for five years or more. In 1932 Jones, of Cleveland, called attention to the possibility of such injuries occurring months and years later in cases which were not malignant. He reported 7 such cases in 520 patients, 6 of whom he cured by surgery. In 1938 Todd, of England, suggested that these injuries were due to a thrombosis of the smaller branches of the hemorrhoidal vessels causing obliteration of the blood supply of the rectosigmoid, thus producing infarctions and ulceration of the mucosa and fibrosis of the muscular coat resulting in constriction of the bowel. Corscaden has reported similar experiences and recommends the amount of radium be reduced and prolonged so as to give the same ultimate amount of irradiation. He suggests 70 mg. for one hundred hours.

Our former average dosage varied from 3,600 to 4,200 mg. hr. In later years it was increased by using, in addition, the colpostat to the perimetrium for 1,800 mg. more. There is a question whether in stepping up the dosage we may have increased the injuries which we are encountering. Corscaden's suggestion may possibly be an answer to the problem, and I believe there has been a definite improvement in his cases. I would strongly urge a more careful follow-up of these cases as intestinal injuries following irradiation are usually a late complication.

seem too hypothetical to believe that the hormonal influences elaborated during gestation could affect both systems in the same manner. As already mentioned, one of the most outstanding evidences of hormonal activation of the urinary tract is that of the marked hypertrophy of the musculature throughout the ureter and especially in its lower end, namely, the sheath of Waldeyer. This cannot be considered a work hypertrophy, for we found these same hypertrophic changes in a patient dying following an operation for an ectopic pregnancy of seven weeks' duration, when it was impossible to have pressure due to the small size of the uterus. Other evidence to support this hormonal theory is presented by the autopsy findings of a man dying from a teratoma of the testicle with generalized metastasis, which proved to be a chorionepithelioma. Prior to operation the urine had been strongly positive for anterior pituitary-like substance on two occasions. The examination of the ureter showed definite hypertrophic changes throughout the entire organ, but was most marked in the juxtavesical portion. Here there was tremendous hypertrophy of the sheath of Waldeyer, the greatest external diameter measuring 8 mm., the measurement of the normal nonpregnant ureter in the same location being about 3.5 mm. Another factor that seems to support the endocrine theory of ureteral activation is that following delivery, and with the rapid decrease of the hormonal content of the urine due to absence of the placenta, the main source of estrogenic and anterior pituitary-like substances, there is a progressive and rather rapid regression of the urinary tract to its normal state.

Knowing of the work of Traut and McLane on ureteral peristalsis during pregnancy, we wished to confirm if possible their observations, for we felt that the peristaltic variations they noted might be dependent upon hormonal influences and not upon muscular work fatigue as might be supposed. If we could demonstrate that these variations were due to hormonal influences, we would then have additional confirmatory data to support this hormonal theory as an etiologic factor in ureteral changes. Traut and McLane have shown that there is an increasing atony of the ureter with advancing pregnancy, and that beginning with the end of the second trimester there is a complete loss of tone, with absence of peristalsis. There is a return of peristalsis just prior to parturition, which then continues on through and after the puerperium.

In order to carry out these experiments, Trattner's hydrophorograph was used. This apparatus was developed in 1922 in order to make a graphic record of the peristalsis of the ureter in situ through the ureteral catheter at the time of cystoscopy. The hydrophorograph is a closed system; the urine from the catheter passes beneath a tambour, and by this means the variations of urinary pressure are clearly recorded on a constantly moving graph. The pressure under which the

Associated with this delayed excretion time there develops an apparent increasing atony of the ureteral musculature.

We believe that dilatation of the ureter is produced by two primary factors: first, changes in the ureter due to hormonal stimulation, as shown by muscular hypertrophy, increased vascularity, and loss of tone. This changed tube then is subjected to the pressure of the semi-cystic, pregnant uterus at the pelvic brim, with resulting dilatation. We feel that if the primary hormonal changes had not taken place, the soft vascular uterus could not exert sufficient pressure on the dense wall of the ureter to produce dilatation.

From histologic studies we have previously shown that the ureter during pregnancy undergoes rather constant and typical changes. One of the most striking of these is the marked muscular hypertrophy of the sheath of Waldeyer, the outer longitudinal layer of musculature, which structure invests the lower 3 to 6 cm. of the pelvic ureters. There is also seen muscular hypertrophy throughout the length of the ureter, confined for the most part to the circular layer. The ureter becomes vascular, soft, dilated, and ribbonlike. The opinion has been advanced that this hypertrophied sheath is the important causative factor in dilatation of the ureter. If this is correct, the dilatations should be bilateral and should begin at the bladder. Our findings have not supported this view, for as already stated, the changes always begin at the pelvic brim and the right ureter is much more affected than is the left. This increased incidence of right ureteral involvement is due to dextrorotation of the uterus, cushioning of the left ureter at the pelvic brim by the overlying sigmoid, and also to the fact that the right ureter crosses the pelvic brim nearly at a right angle, making it more vulnerable to pressure. The left ureter runs into the pelvis in much more of a straight line and is consequently less subject to pressure effects. We believe the vast majority of investigators are now of the opinion that dilatation of the ureter at the pelvic brim is due to pressure, this being the theory originally presented by Opitz in 1905. We felt that this theory was definitely proved by the experiments we conducted with the use of the indwelling catheter during the later stages of pregnancy. It was shown that if continuous drainage of the upper urinary tract with the indwelling catheter was maintained for forty-eight to seventy-two hours, there was a definite regression of the dilated pelvis and abdominal ureter. Further confirmatory data were added by our studies of the dilatation changes occurring in the presence of large pelvic tumors, especially those of long standing and those conforming to the contour of the pregnant uterus.

Is there sufficient evidence to support our belief that the urinary tract is subject to hormonal stimulation? We feel that the following data support our opinion that this activation does play a definite role.

When one considers the embryologic development of the generative and urinary systems, both arising from the same anlage, it does not



In order to ascertain the normal ureteral rhythm, a study of 8 patients with no generative or urinary pathology was carried out. As will be noted, the tracing is made with three variations of pressure, namely, at 15, 10, and 5 cm. of water (see Fig. 1, *a*, B.S.). This hydrophorographic tracing of the normal nonpregnant woman shows regular rhythmicity and amplitude of the contraction waves, the contraction phase about equaling the period of relaxation. The tracing was approximately the same at the various pressure levels. There was rapid excretion of urine.

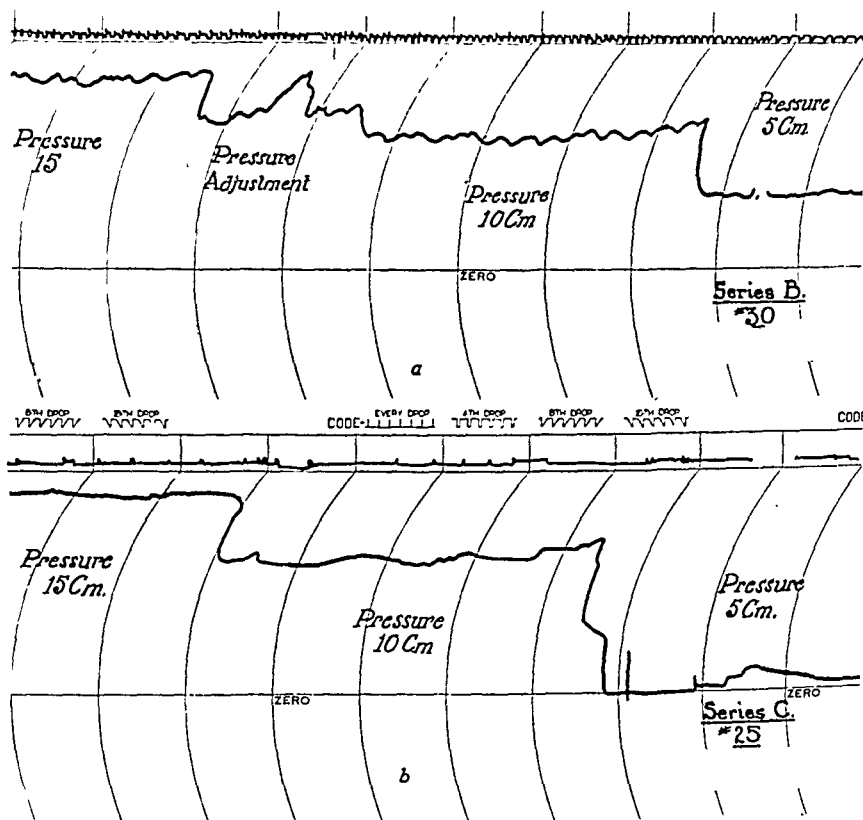


Fig. 2.—*a*, S.C. (b-18). First pregnancy, twenty weeks' gestation. *b*, J.E. (b-20). First pregnancy, thirty weeks' gestation.

After having established the curve for a normal nonpregnant woman, a study of the variations during pregnancy and the puerperium was undertaken; 17 patients were examined during the first trimester, 31 during the second, 46 during the third, 15 of these just prior to delivery, and 12 during the puerperium, making a total of 106. These readings were not conducted consecutively on each patient throughout the several trimesters of pregnancy, for we felt that it might be of greater value to determine the various trimester variations, if any existed. During the early part of the first trimester, the peristaltic wave showed a slight variation in its behavior from that of the nonpregnant control, as evidenced by beginning loss of ureteral irritability, which continued and increased throughout this phase (see Fig. 1, *b*, L.Z., third pregnancy, nine weeks' gestation). With the progress of the second trimester there is an increasing loss of tonus, especially marked with

urine flows is regulated by a valve and measured with a manometer, and the frequency of the drops of urine is recorded electrically. A point of practical value is that with the increased intake of water there is a decrease in concentration of sodium chloride ions, thus interfering with the function of the magnetic counter. This difficulty was overcome by placing a tablet of sodium chloride in the tambour chamber, thus increasing the ionization and permitting proper functioning of the drop recorder.

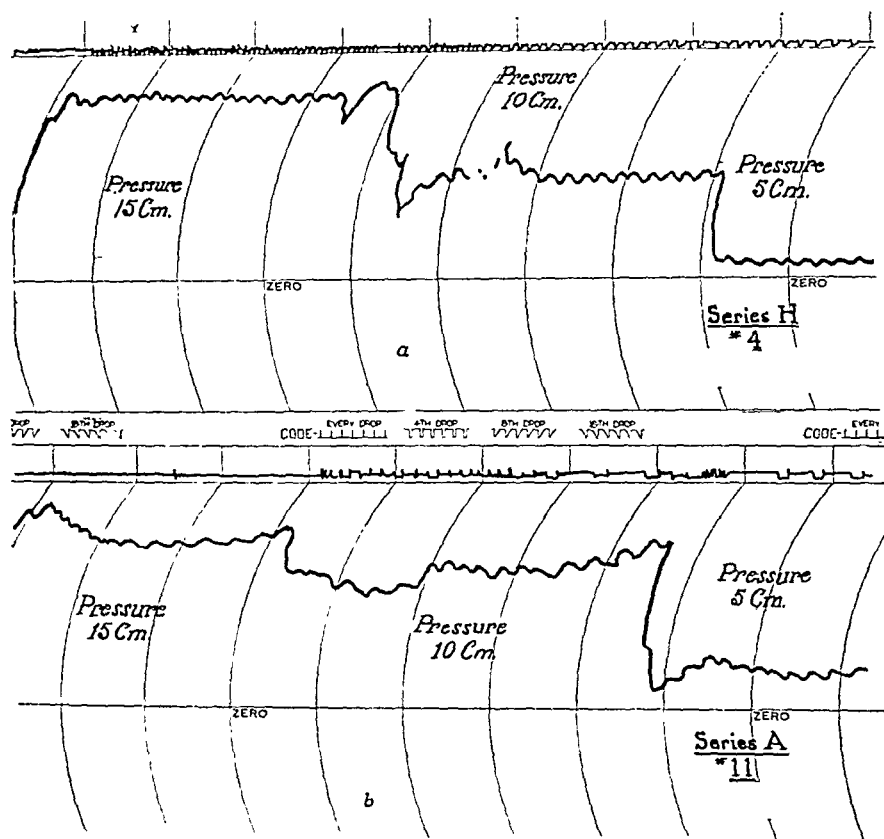


Fig. 1.—a, B.S. (b-47). Hydrophorographic tracing, normal patient. b, L.Z. (b-25). Third pregnancy, nine weeks' gestation.

The technique of obtaining the tracing was as follows, and was constant throughout the entire study. Each patient received 1,000 c.c. of water one-half an hour previous to the examination, so that active peristaltic behavior would be assured. A water cystoscopy was then done, with the patient in the lithotomy position. The right ureter was catheterized, the catheter marked at 11 cm. and introduced into the ureter up to that point. The cystoscope was then clamped in place so that frequent inspection of the catheter in the ureter during the experiment was possible. The catheter was attached to the apparatus and the instrument placed between the patient's legs; care was taken to see that the kidney pelvis and the tambour were on the same level (see Fig. 2). None of the patients received any sedation, as it was thought that this might interfere with ureteral peristalsis.

there is a resurgence of ureteral activity (see Fig. 3, *a*, H.C., third pregnancy, thirty-ninth week of gestation). Here is noted a definite return of ureteral irritability. During the post-partum period, it is noted that the contraction wave is more regular but there is still evidence of lessened tonus (see Fig. 3, *b*, L.M., first pregnancy, fifth day). Throughout this study considerable variation in the contraction waves at the various pressures was observed. However, it was rather constantly noted that the tracings obtained under 5 cm. of pressure showed quite a low amplitude of peristaltic activity. The explanation of this fact is probably due to there being an insufficient head of pressure, with a resulting decrease of muscular contraction of the ureter. The accompanying composite graph gives a graphic portrayal of the decreasing ureteral tonus during the advance of pregnancy, and also the return of ureteral activity prior to parturition (Fig. 4).

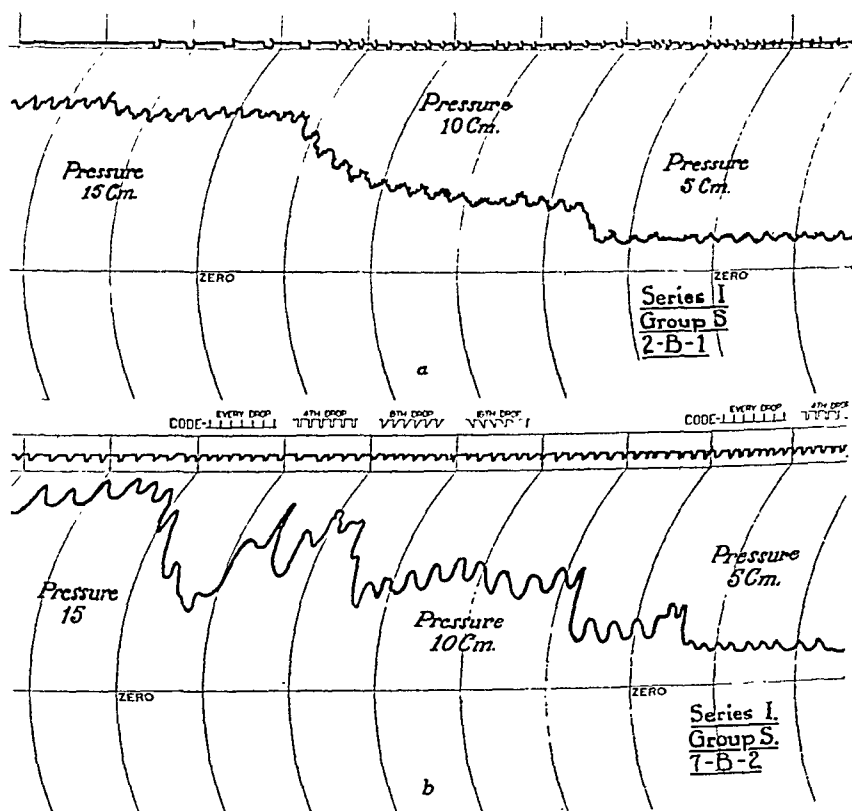


Fig. 5.—*a*, J.H. (b-37). Base line tracing before treatment with stilbestrol. *b*, After one week of treatment with stilbestrol 2 mg. twice daily.

After completing this study of ureteral behavior during pregnancy and observing the very striking atonia that developed, we then attempted to prove that the peristaltic activity and atony were dependent upon hormonal influences. We know that during pregnancy large amounts of estrogenic and progestogenic substances are elaborated in the placenta. The estrogenic substance produces growth and also causes contraction of the uterus, whereas, it is generally thought that the progestogenic substance allays uterine activity. By priming normal women with large and prolonged doses of estrogenic and progesto-

the pressure of 5 cm. (see Fig. 2, a, S.C., first pregnancy, twenty weeks' gestation). Here practically no peristaltic activity is noted. There is rapid excretion of urine. During the third trimester complete loss of tone develops (see Fig. 2, b, J.E., first pregnancy). No contraction waves are seen at the various pressure levels. Just prior to parturition

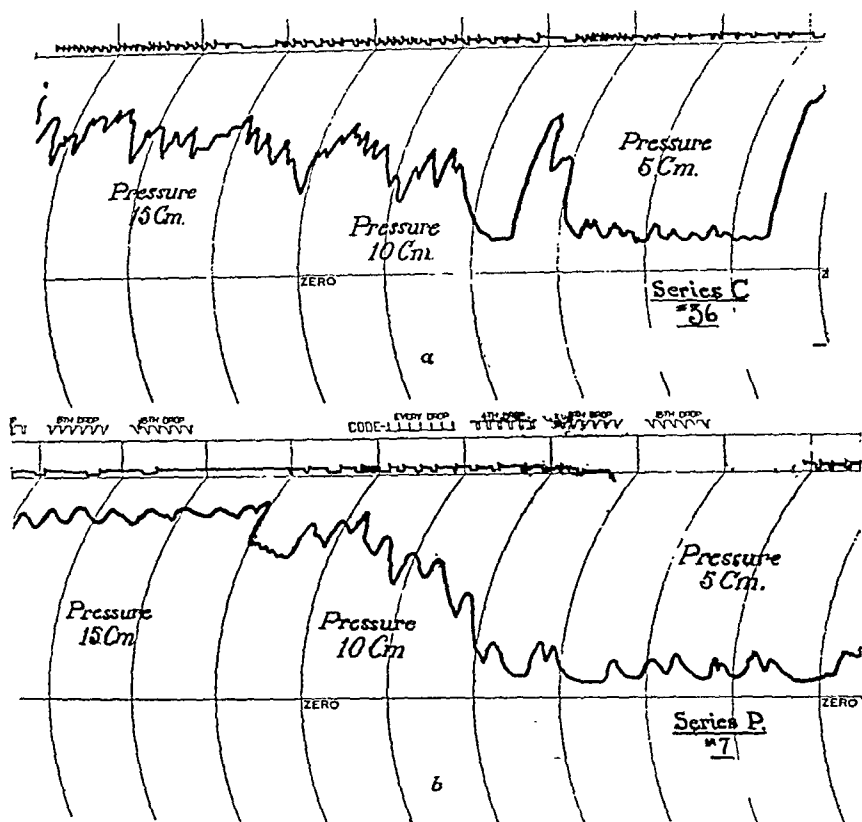


Fig. 3.—a, H.C. (b-43). Third pregnancy, thirty-nine weeks' gestation. b, L.M. (b-23). First pregnancy, fifth post-partum day.

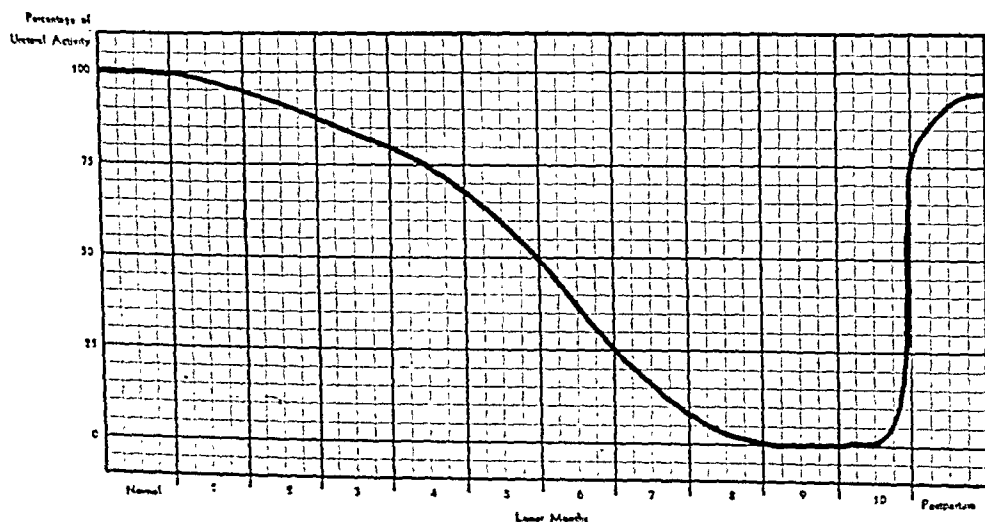


Fig. 4.—Ureteral peristalsis during pregnancy.

c. After two weeks of estrogenic therapy, no very definite activation is seen here. (Fig. 6.)

d. After three weeks of estrogenic therapy, decided increase of ureteral activity is noted. With lowering of the pressure there is seen a decrease in the number of contraction waves.

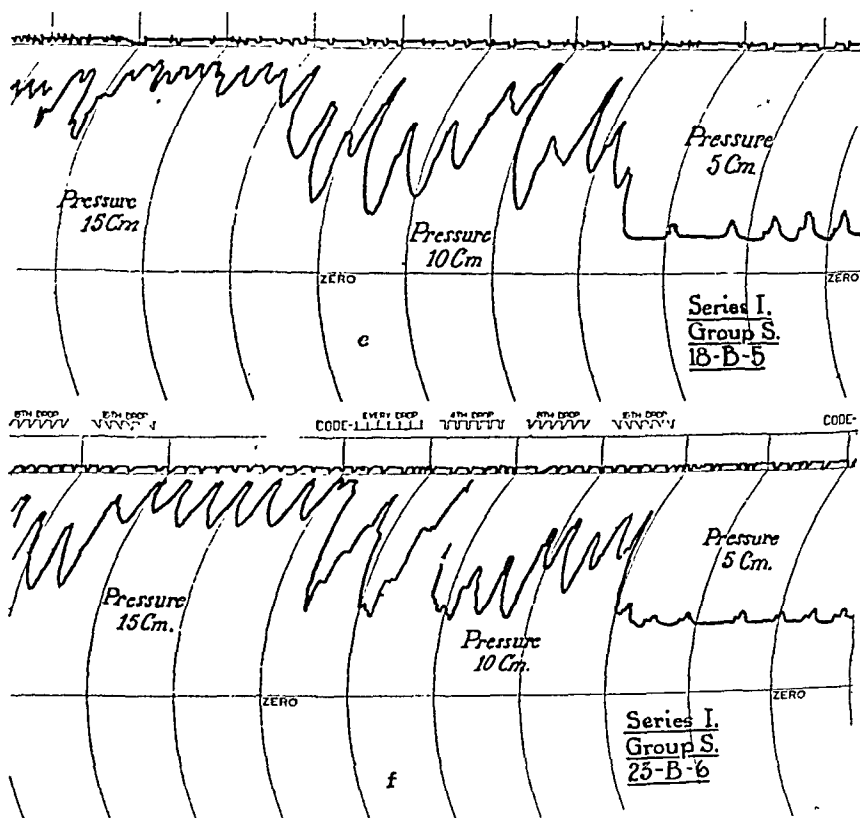


Fig. 7.—c, J.H. (b-37). After four weeks of treatment with stilbestrol 2 mg. twice daily. f, After five weeks of treatment with stilbestrol 2 mg. twice daily.

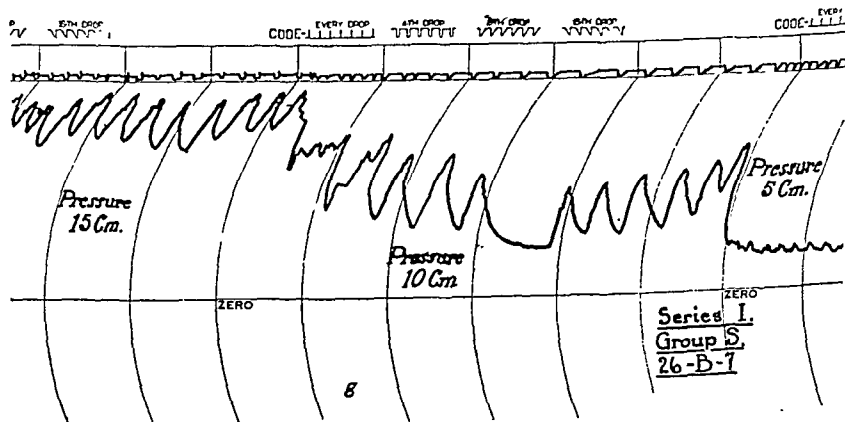


Fig. 8.—g, J.H. (b-37). After six weeks of treatment with stilbestrol 2 mg. twice daily.

e. After four weeks of estrogenic therapy, there is noted a very marked increase in amplitude of the contraction waves, particularly in the 10 and 5 cm. pressure zones. There is good urinary excretion. (Fig. 7.)

genic substances, we hoped to simulate in a measure hormonal conditions that exist during pregnancy and possibly produce the same ureteral behavior that normally occurs during this period. The experiments were carried out in the following manner:

Eight normal women, the average age being 34, with no urinary or generative pathology, were treated with stilbestrol, each receiving orally 2 mg. twice daily, over a period averaging ten weeks, the patients thus receiving a total of 280 mg. This large dosage produced no

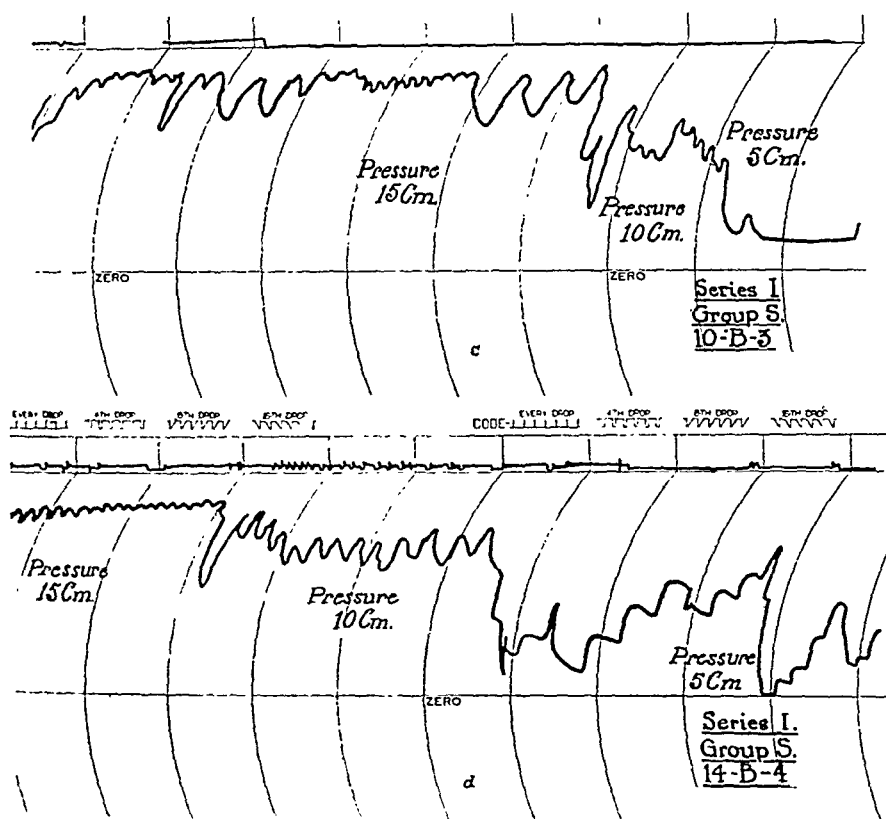


Fig. 6.—c, J.H. (b-37). After two weeks of treatment with stilbestrol 2 mg. twice daily. d, After three weeks of treatment with stilbestrol 2 mg. twice daily.

untoward effects except for slight nausea in several of the patients. Weekly, hydrophorographic tracings were made and, as will be noted, very marked peristaltic activity was produced. The amplitude of the contraction waves was far greater than those seen in the control non-primed patient. As the period of therapy progressed, the ureteral activity became more marked, being quite exaggerated in the last weeks of the experiment (see Figs. 5 to 8).

a. Normal, nonpregnant patient (Fig. 5), base line tracing before treatment with stilbestrol, showing normal ureteral behavior, with active excretion of urine. Throughout the following experiment this patient received stilbestrol, 2 mg. orally twice daily, receiving a total of 140 mg.

b. After one week of estrogenic therapy, there is noted definite increase of ureteral irritability, especially in the 15 and 10 cm. pressure zones. There is good urinary excretion.

b. After one week of progestogen therapy, there is seen a definite lessening of ureteral activity as shown by the decrease in amplitude as well as in the frequency of contractions. In the low pressure zone very little tonus is seen.

c. After two weeks of progestogen therapy, the changes are not markedly different from the previous graph. (Fig. 10.)

d. After three weeks of this same progestogen therapy, there is seen increasing loss of tonus, especially marked in the 5 cm. pressure zone.

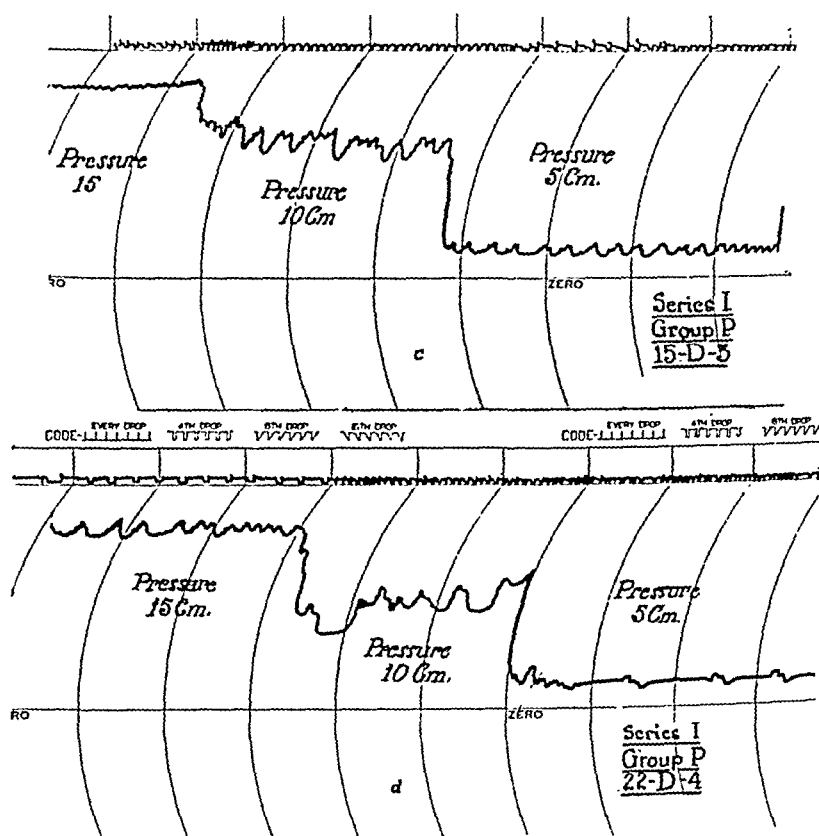


Fig. 10.—c, W.H. (b-29). After two weeks of treatment with proluton, 8 mg. q.w. and pranone, 40 mg. q.d. d, After three weeks of treatment with proluton, 8 mg. q.w. and pranone, 40 mg. q.d.

e. After four weeks of progestogen therapy, there is nearly complete atonia, most marked in the low pressure zone. The urinary excretion is somewhat lessened. (Fig. 11.)

f. After five weeks of progestogen therapy, complete atonia is observed, especially in the 10 and 5 cm. zones. As will be noted, there is no evidence of urinary output. Urine was excreted, but due to a breakdown in the magnetic timer it was not recorded.

It would seem from these two experiments that hormonal influences play a definite role in ureteral behavior, the estrogenic substance activating the peristaltic contractions and the progestogenic substance allaying these contraction waves.

As we have shown, the peristaltic activity of the ureter during pregnancy may be dependent upon estrogenic and progestin effects. However, from the work of Cohen, Marrian, and Watson it is possible that

f. After five weeks of estrogenic therapy, a continuation of the marked peristaltic activity is seen in the 15 and 10 cm. zones. Very little activity is seen with the 5 cm. pressure. There is good urinary excretion.

g. After six weeks of treatment with the same estrogenic therapy, even more marked peristaltic contractions are seen here and, as in the previous graph, there is little activity in the lower pressure zone. (Fig. 8.)

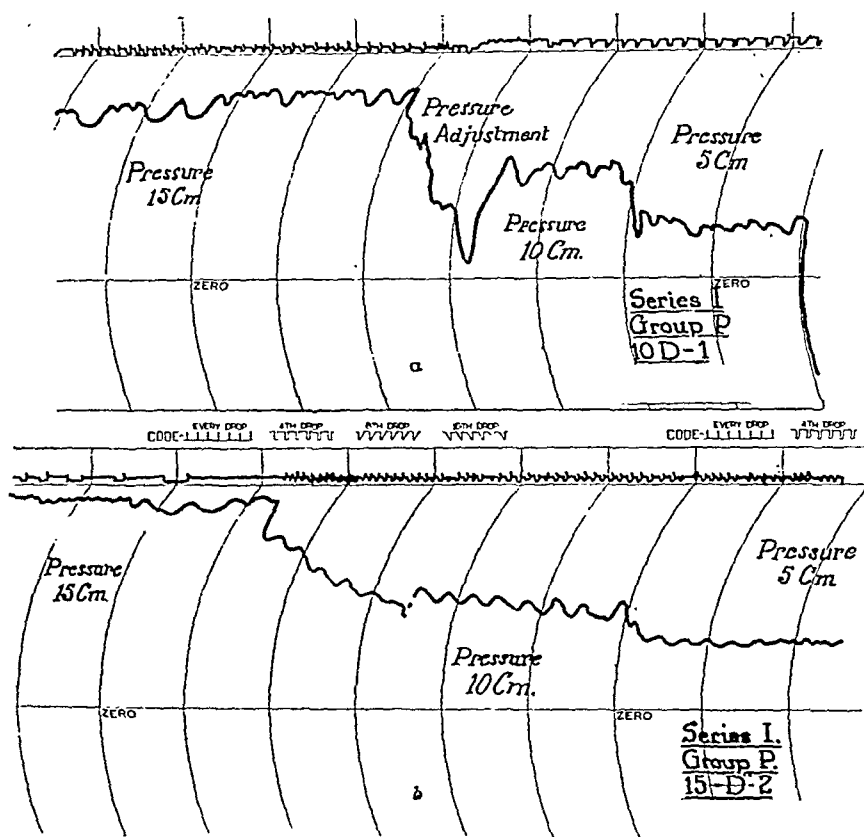


Fig. 9.—a, W.H. (b-29). Base line tracing before treatment with proluton and pranone. b, After one week of treatment with proluton, 8 mg. q.w., and pranone, 40 mg. q.d.

In order to determine if allaying of ureteral activity and final atonia developed under the influence of a progestogenic substance, another group of 8 normal women with no urinary or generative pathology was selected, their average age being 31 years. These women received an intensive course of progestogenic therapy over a period of nine weeks, each receiving weekly proluton 8 mg. intramuscularly, and in addition, pranone 280 mg. orally, making a total dosage that each received proluton 72 mg. and pranone 2,520 mg. No symptoms referable to this intensive therapy were demonstrable. Weekly hydrophorographic tracings were made and, as will be noted in the following graphs, there was a gradual decrease in the amplitude of the peristaltic waves. The diminution of activity increased with the duration of the therapy (see Figs. 9 to 11).

a. Base line tracing of normal nonpregnant woman prior to progestogen therapy. This graph is not as satisfactory as the two previous controls above shown. Throughout the following experiment this patient received proluton 8 mg. a week hypodermically, and pranone 40 mg. a day orally. (Fig. 9.)



From these observations it has been shown that after the third month of pregnancy there is an increasing amount of the combined estrone and estriol excreted in the urine. The estrogens in this state are of low physiologic activity, whereas, it is thought that the free forms may have definite oxytocic properties. As will be noted from our investigations of peristaltic variations during pregnancy, it is in this period, namely from the third month on, that an increasing diminution of activation comes about, until in the third trimester there is complete atonia existing. It is possible that this atonia may be brought about by the inactivity of the increasing physiologically impotent combined estrogen. The absence of contraction waves continues up to just before parturition, when there is a resurgence of peristaltic activity which goes hand in hand with a pronounced decrease in the combined forms and an associated increase in the free estrogen. These free estrogens, having oxytocic properties, may exert their influence on the ureter and cause its reactivation. This work of Cohen, Marrian, and Watson offers an attractive explanation of ureteral behavior. However, as such a divergence of opinion exists in regard to estrin excretion during pregnancy, the possible relationship can only be speculative.

#### DISCUSSION AND SUMMARY

We have shown in previous communications that dilatation changes in the urinary tract are of frequent occurrence, also that typical histologic alterations are noted, for the most part, those of muscular hypertrophy, hyperemia, and increased vascularity. The most striking change observed was the great hypertrophy of the sheath of Waldeyer. We feel that there are two etiologic factors that produce these alterations, i.e., hormonal influences and pressure effects. That hormonal influences do play a role in the ureteral changes is sustained by the following facts: that definite hypertrophic changes do occur in the ureter during pregnancy and also that similar alterations have been observed in the male ureter, the patient dying from a teratoma of the testicle with metastatic chorionepithelioma. With the advance of pregnancy there is an apparent atony of the ureter observed, which belief induced us to study ureteral peristalsis during the various phases of gestation. A summary of this study, determined upon 130 normal pregnant women, showed that during the early part of the first trimester the peristaltic behavior of the ureter was nearly similar to that occurring in the nonpregnant woman. However, as pregnancy progressed there was noted a continued and gradual decrease in the frequency as well as in the amplitude of the contraction waves, until in the seventh and eighth months a complete atonia existed. This atonic state continues up to a short time before delivery. There was then noted a return of the same peristaltic activity as seen during the latter part of the first trimester. In the belief that these variations of ureteral behavior were engendered by hormonal stimulation, we made hydro-

these variations in behavior may also be entirely due to estrogenic effects. These investigators have developed a procedure for the quantitative assay by colorimetric methods of estrone and estriol, both in the combined and free forms, occurring in human pregnant urine. They have shown that after the third month of pregnancy there is a rapid increase in the amounts of combined estrone and estriol excreted in the urine. After the sixth month the rate of increase becomes greater, so

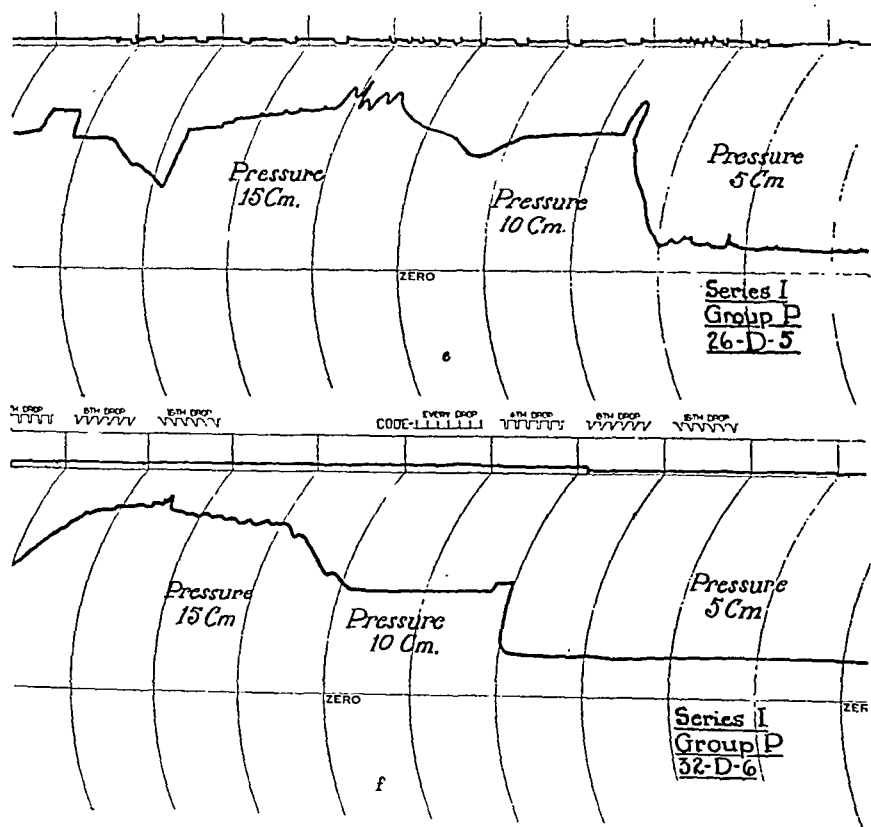


Fig. 11.—*e*, W.H. (b-29). After four weeks of treatment with proluton, 8 mg. q.w. and pranone, 40 mg. q.d. *f*, After five weeks of treatment with proluton, 8 mg. q.w. and pranone, 40 mg. q.d.

that about one week prior to parturition there is a daily average excretion of 22 mg. of combined estriol and 3 mg. of estrone. They also state that the average curves of these combined estrogens show a decided decrease just before delivery. In regard to the free estrogens, these substances, estrone and estriol, are at a consistently low level during the first eight months of pregnancy, never reaching more than 1 per cent of the amounts of the respective combined forms. Shortly before parturition there is an increase of these free forms excreted in the urine. This increase occurs about the same time that there is a decrease of the combined forms. During the first twenty-four hours following parturition, the quantities of the free form excreted in the urine exceed those of the combined forms, after which they both rapidly decrease and in forty-eight hours are excreted in very small amounts.

presented urographic evidence of ureteral alterations in the form of either obstruction, displacement, or both.

Dr. Hundley's findings plus this study have suggested another approach to the problem of the pregnant ureter. By using selected patients with myomas, who already present urographic evidence of ureteral disturbance, we propose to test the effects of the estrogenic and luteal secretions upon these structures. Thus we may be able to produce the ureteral changes of pregnancy by artificial means, thereby taking another step in the solution of this interesting problem.

DR. HERBERT F. TRAUT, NEW YORK, N. Y.—In this very interesting study by Dr. Hundley and his associates, it has been demonstrated that the peristaltic activity, and perhaps also the tonicity, of the ureteral musculature can be influenced in the nonpregnant state. Estrogenic substances have been shown to accentuate peristalsis, whereas progesterone has been shown to have a quiescent effect.

Ever since 1848 when Rayer first described the dilated ureters of pregnancy, speculation occurred about the cause of this phenomenon. As a result of many studies, gradual progress has been made toward an answer. As has been shown in this study, ovarian hormones in the nonpregnant woman may have a very marked influence on the ureters. However, we are still in the dark as to the mechanism affecting them in pregnancy. The outstanding characteristic in the ureter of the pregnant woman is the disappearance of muscular irritability followed by dilatation of the tract. Inasmuch as progesterone, at least of corpus luteum origin, and possibly of other origins as well, does not increase in titer in the blood stream after the fourth month of pregnancy, whereas the atony of the ureter reaches its peak at the sixth or seventh month, it would seem very likely that in the pregnant woman there must be other substances which have an effect upon the ureter similar to that which Hundley and his associates have shown progesterone to have.

Furthermore, it is very interesting to know that estrogens, to be specific, estradiol benzoate and stilbestrol, in therapeutic dosage do not produce in the pregnant woman of five to six months' pregnancy increased peristalsis. This statement is made as a result of several attempts to induce better drainage of the urinary tract in pregnant women suffering from pyeloureteritis.

It would seem, therefore, that there are still some steps to be taken before we can know the whole mechanism involved in producing atony of the ureter and stasis of urine in the pregnant woman.

I wish that Dr. Hundley and his associates might have included pregnant women in their studies. One particular obstacle has disappeared from this problem with the advent of the sulfa drugs. At the time we worked on this we had no way of controlling urinary infection in pregnancy except to terminate the pregnancy in the more serious cases. With the sulfa drugs we can cure the upper urinary tract infections and take care of the stasis and atony which we were never able to accomplish before.

phorographic tracings of normal women who had been subjected to intensive estrogenic and progestogenic therapy. Marked activation of ureteral peristalsis was noted in the group that received stilbestrol, while definite allaying of the contractions was produced by proluton and pranone.

From these observations it would seem that estrogenic substances activate the ureter and progestogenic substances allay this activity.

We wish to express our appreciation to Dr. Louis H. Douglass, Professor of Obstetrics, University of Maryland, for his wholehearted cooperation. We are also indebted to Abbott Laboratories for the supply of stilrone (stilbestrol) and to the Schering Corporation for the proluton and pranone.

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#### DISCUSSION

DR. FRANKLIN L. PAYNE, PHILADELPHIA, PA.—We are led to believe that common alterations of the ureter in pregnancy are, in part, the result of hormonal stimulation. This theory is supported by the work of Van Wagenen and Jenkins who found urographic evidence of unilateral dilatation in 6 out of 10 pregnant Rhesus monkeys. Cesarean sections were done upon 2 of these animals, with delivery of the fetus, and the retained placentas remained intact for approximately three months. During this time urograms showed ureteral dilatation to indicate that this change is "related primarily to the state of pregnancy and secondarily to the weight of the uterus."

In the current paper, the tracings showing ureteral response to the estrogens and to progesterone are most convincing. Apparently urographic studies were not made during this investigation. With controls prepared from the same patients prior to hormone medication, it would have been interesting to see if their ureters were sufficiently affected by these substances to produce urographic changes.

The results of the essayist's experiments point so clearly to estrogen-progesterone imbalance as the hormonal basis of ureteral behavior during pregnancy that it seems a pity to introduce the Cohen-Marrian theory. This pre-labor reversal of the combined and pure estrogens is still open to question. Even if it is true, its application to the present problem is not valid as an explanation of ureteral atony or subsequent resumption of tone. Throughout the latter part of pregnancy the urinary content of the free (active) estrogens does not fall below, but in fact exceeds that of the nonpregnant state, when ureteral peristalsis remains normal.

In addition, there is abundant clinical evidence of estrogenic activity during pregnancy, as we all know. Furthermore, both the characteristic changes of the pregnant ureter and the delayed post-partum return to normal suggest the response of tissue to a positive stimulus and not the reaction of deprivation.

While this contribution emphasizes the importance of hormone influence in ureteral atony, it does not deny the role of extrinsic pressure in the development of ureteral dilatation. That such pressure does produce changes in the absence of pregnancy was shown by Dr. Hundley previously and confirmed by us in a recent study. Of 96 patients with benign pelvic tumors varying in size from three and one-half to eight months' pregnancy, we found that 66 (69 per cent)

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women are in the child bearing age the blood supply to the involved area tends to be good and the tissues healthy. The postoperative fistula on the other hand, is more commonly seen in older women often past the menopause. The lesion is characteristically small and generally located in a vaginal scar. Since most of the postoperative fistulas follow hysterectomy, they are often inaccessibly located high in the vagina.

In 1935<sup>3</sup> we reviewed the world literature on vesicovaginal fistula. Our present report is based on a study of the literature for the past decade and on experience gained through treatment of 51 cases during the past ten years.

Countless methods and technical variations thereof have been proposed for the correction of these fistulas. Many techniques are best suited for the now uncommon puerperal lesions. Doubtless the extensive loss of tissue and scarring made repair of some larger openings extremely difficult. In our experience, however, the puerperal vesicovaginal fistula, though larger, is accessible and generally more easily repaired than the present-day smaller postoperative lesion.

In the past a good deal of emphasis has been placed on preparation of the patient. This is important but it does not compensate for lack of preparation on part of the surgeon. Since the chances for cure decreases with each operation due to the increased scarring and diminished blood supply, the surgeon should not underestimate the task before him. A small opening may be more difficult to close than a larger one. The operator should have at his command an adequate understanding of the problem. Such understanding when combined with careful preparation of the patient may be expected to result in successful closure in the majority of cases.

Preparation of the patient while aimed primarily at obtaining healthy tissue in the operative field also includes general upbuilding regimen and precise localization of the lesion. Extremely small openings may be localized by air insufflation of the bladder as suggested by M. L. Stadiem<sup>1</sup> or by the instillation of a dye such as methylene blue. Visualization from the bladder side should also be carried out in order to determine the relative position of the fistula in relation to the ureteral orifices and the bladder neck. If the fistula and ureter are in close proximity the latter may be injured at the time of repair. When the fistulous opening is large the vaginal placement of a cervical (obstetric) bag of the Fillis type has been recommended by Angel.<sup>2</sup> This plugs the opening and permits distention of the bladder for cystoscopic study.

From the bladder side most of the fistulas are seen to lie in or near the trigone. Local preparation may also require a preliminary clearing away of redundant mucous membrane tags or incision of scar tissue in order to make surgical correction the easier. This type of surgical preparation is not utilized often enough. The preliminary clearing of the field and incisional mobilization of adjacent tissues to permit approximation without tension later is an important preparatory step

## THE SURGICAL TREATMENT AND POSTOPERATIVE CARE OF VESICOVAGINAL FISTULA\*

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DURING the past ten years there have appeared approximately 150 published reports on vesicovaginal fistula. Some of these are single case reports while others include long lists of patients treated. Probably not more than two-thirds of all vesicovaginal fistulas are reported. This does not mean the lesion is common, but it does indicate the subject is far from being a closed book. Indeed, there is reason to believe that vesicovaginal fistula is still very much a contemporary though altered problem. Altered with respect to size of the fistulas, accessibility, and etiology. Time was when most fistulas of this type occurred as a result of long and arduous labor, but all that changed with a better understanding of the mechanism of labor and improved obstetric care. Today the most productive source of vesicovaginal fistula is pelvic surgery. Probably more than two-thirds of these fistulas are the result of pelvic operation, especially hysterectomy. Ample proof on this point may be found in most of the contemporary articles on the subject. Furthermore, it is not unlikely that during this period of international stress caused by World War II, the incidence will actually increase. Certainly with more pelvic surgery performed by less experienced surgeons this is not beyond the realm of possibility. Doubtless the increasing number of hysterectomies and the present enthusiasm for total extirpation significantly contribute to this situation. It is axiomatic that in correcting one disease we must not cause another. Yet, this is happening and it is occurring too frequently. There are too many urinary tract injuries at the time of pelvic surgery. There are too many vesicovaginal fistulas following too many hysterectomies.

Obviously damage to the urinary tract cannot always be avoided, but when 70 per cent of the hundreds of fistulas reported in the past decade occurred subsequent to pelvic surgery and especially hysterectomy, it is questionable whether physicians performing the hysterectomies possess the necessary knowledge and skill which should enable them to minimize trauma to the urinary tract.

Post obstetric fistulas are more often seen in young adults, usually healthy except for the fistula. Generally the opening is large, but accessible when traction is exerted on the cervix. Because most of these

\*Read at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.

TABLE I.

| SERIES NO. | HOSPITAL NO. | AGE | SIZE   | CAUSE                     | NO. PREV. OPERATIONS | RESULT HERE | COMPLICATIONS                                       |
|------------|--------------|-----|--------|---------------------------|----------------------|-------------|---|
| 1          | 275586       | 36  | Large  | Delivery                  | 1                    | +           |   |
| 2          | 292516       | 51  | Small  | Supravaginal hysterectomy | 0                    | +           |   |
| 3          | 300544       | 40  | Medium | Hysterectomy              | 0                    | +           |   |
| 4          | 300259       | 24  | Small  | Delivery                  | +                    | +           |   |
| 5          | 294066       | 51  | Small  | Vaginal hysterectomy      | 0                    | +           |   |
| 6          | 325938       | 45  | Small  | Total hysterectomy        | 2                    | +           |   |
| 7          | 348845       | 19  | Small  | Delivery                  | 0                    | +           |   |
| 8          | 348445       | 49  | Small  | Total hysterectomy        | 0                    | +           |   |
| 9          | 346589       | 33  | Large  | Delivery                  | 7                    | -           |   |
| 10         | 346488       | 34  | Medium | Delivery                  | 0                    | +           |   |
| 11         | 338120       | 26  | Small  | Delivery                  | 0                    | +           |   |
| 12         | 331017       | 27  | Small  | Delivery                  | 1                    | +           |   |
| 13         | 370193       | 28  | Large  | Delivery                  | 0                    | +           |   |
| 14         | 353155       | 24  | Small  | Delivery                  | 1                    | +           |   |
| 15         | 227961       | 39  | Small  | Plastic                   | 1                    | +           |   |
| 16         | 338266       | 49  | Medium | Plastic                   | 1                    | +           |   |
| 17         | 390743       | 44  | Small  | Total hysterectomy        | 2                    | -           |   |
| 18         | 390199       | 44  | Large  | Plastic                   | 2                    | -           | Diabetes<br>Healed with<br>cautery. No<br>operation |
| 19         | 378232       | 52  | Small  | Total hysterectomy.       | 0                    | +           |   |
| 20         | 375454       | 45  | Small  | Hysterectomy              | 4                    | +           |   |
| 21         | 402406       | 44  | Small  | Delivery                  | 0                    | +           |   |
| 22         | 418086       | 60  | Medium | Vaginal hysterectomy      | 0                    | +           | Bronchopneu-<br>monia                               |
| 23         | 420563       | 36  | Large  | Delivery                  | 2                    | +           |   |
| 24         | 429384       | 52  | Small  | Supravaginal hysterectomy | 2                    | +           |   |
| 25         | 422472       | 51  | Large  | Vaginal hysterectomy      | 0                    | +           | Died of pul-<br>monary embo-<br>lus, 18th day       |
| 26         | 434647       | 52  | Small  | Plastic                   | 2                    | +           |   |
| 27         | 344944       | 49  | Medium | Plastic                   | 0                    | +           | Pulmonary em-<br>bolus                              |
| 28         | 443482       | 43  | Small  | Delivery                  | 1                    | +           |   |
| 29         | 448118       | 53  | Large  | Radium                    | 0                    | -           |   |
| 30         | 448389       | 67  | Medium | Total hysterectomy        | 0                    | +           |   |
| 31         | 450756       | 43  | Medium | Hysterectomy              | 3                    | +           |   |
| 32         | 440296       | 41  | Medium | Delivery                  | 2                    | +           |   |
| 33         | 451870       | 49  | Small  | Hysterectomy              | 0                    | +           |   |
| 34         | 451372       | 27  | Medium | Delivery                  | 5                    | +           |   |
| 35         | 276992       | 68  | Small  | Total hysterectomy        | 0                    | +           |   |
| 36         | 438646       | 24  | Medium | Delivery                  | 2                    | +           |   |
| 37         | 436629       | 49  | Large  | Bladder stone             | 3                    | +           | Thrombophlebi-<br>tis                               |
| 38         | 345882       | 24  | Medium | Delivery                  | 1                    | -           |   |
| 39         | 456973       | 45  | Small  | Hysterectomy              | 0                    | +           |   |
| 40         | 470335       | 42  | Large  | Hysterectomy              | 1                    | +           |   |
| 41         | 466403       | 35  | Large  | Total hysterectomy        | 0                    | +           |   |
| 42         | 456819       | 42  | Large  | Vaginal hysterectomy      | 1                    | -           |   |

in some of the more difficult, many times operated, badly scarred cases. In all cases an acid urine should be maintained.

Since many of the postoperative fistulas occur in postmenopausal women, 37 per cent in our series, it has been our practice to administer an estrogen for some time before and after operation, generally 0.5 to 1.0 mg. stilbestrol daily. We believe this aids healing by increasing the capillary circulation and epithelization of the vaginal mucous membranes.

Judging from the recorded opinions of many recent writers on this subject and our own experience, there is no one approach or technique of repair suitable for all cases. As in all branches of surgery the technique must be varied to best meet the requirements of the individual patient.

The use of the indwelling catheter immediately postoperative will aid in permitting the closure of many bladder fistulas. From the reports of Deutschmann,<sup>4</sup> Apajalahti,<sup>5</sup> O'Connor,<sup>6</sup> and Thompson,<sup>7</sup> it appears that the usefulness of the catheter as a means of curing postoperative bladder fistula has not yet been fully realized. Prolonged use may not only lead to cure but also aids in restoring the tissues to normal before surgery is instituted.

In all cases here reported the vaginal approach was utilized. Formerly the transvesical and transperitoneal approaches were also used, but since the vaginal route has proved increasingly satisfactory, we have had less and less occasion to resort to these other acceptable methods. While most operators prefer the vaginal route, it must be recognized that good results are also obtained by the other methods. The surgeon interested in the repair of vesicovaginal fistula should be familiar with all procedures, for there is always the odd case that can best be treated by variations of what appears to be a standard method of treatment.

While the vaginal approach was utilized in all of our present series, we are not blind to the merits of either the transvesical or transperitoneal approach. Our preference for the vaginal route is attributed to: (1) Ease of visualization and repair, (2) less trauma and danger to the patient, (3) greater postoperative comfort, and (4) the patient may be ambulatory on the third to fifth postoperative day.

In utilizing the vaginal approach the patient is placed in the inverted Trendelenburg position which permits convenient exposure of the opening. This position with modifications has been profitably used for almost one hundred years and in our opinion is still well suited for most cases.

For the majority of postoperative vesicovaginal fistulas, the so-called split flap technique is preferred. There are many variations of this, but in general it consists of making an incision around the fistulous opening and separating the vaginal from the bladder mucous membranes for approximately one-half inch around the fistula. The bladder mucous



7. Capillary bleeding as evidence of a good blood supply should be a welcome sight. This can be controlled during operation by the use of tiny adrenalin dipped sponges. Excessive bleeding may jeopardize the ultimate outcome and must be controlled.

Postoperative care is important and it is in this connection that our own technique has undergone greatest change in the past ten years.

The use of an indwelling catheter seems desirable but if the fistulous site is near the bladder neck or if the catheter is likely to traumatize the repaired area frequent catheterization with a small straight catheter may be preferable. Similarly suprapubic drainage may be desirable in this connection.

Keeping the patient in the prone position is logical and helpful for reasons already abundantly recorded. When maintained for any length of time, however, this position, whether it be on a Bradford type of frame or on a split mattress, becomes extremely uncomfortable, and even harmful. In addition to the physical discomfort there is disturbed physiology due to the curtailed activity, limited food intake and restricted bowel function. These factors may definitely interfere with the patient's healing ability. Furthermore, there is reason to believe that the prolonged prone position predisposes to embolism. In the past when we kept our patients in this prone position for ten days, massage and movement of the arms and legs were always emphasized. Yet, in spite of this, two of the 51 patients in this series developed pulmonary emboli and one patient died of this complication. Since this happened and partly on the suggestion of Dr. L. Emge and Dr. Albert Pettit of San Francisco, we have kept our patients in the prone position on a split mattress for only two to four days following which the patients are permitted up. Food and drink are allowed as soon as tolerated. The indwelling catheter is removed on the fifth to tenth day and the patient discharged on the twelfth to fourteenth day. This altered postoperative care has made a tremendous difference in the comfort of patients and on the basis of our experience has in no way jeopardized the healing.

The 51 patients treated by us during the past ten years are listed in Table I.

The results in this series show 43, or 85 per cent, cured and 8, or 15 per cent, complete or partial failures.

Experience gained from the treatment of vesicovaginal fistula during the past ten years and a review of the literature during this time warrant the following observations:

1. Familiarity with the technical problems involved and remedial methods available is desirable on the part of any surgeon contemplating the repair of vesicovaginal fistula.

2. Surgical repair should not be undertaken until the involved tissues present a healthy appearance. Excision of mucous membrane tags and the incision of scar tissue to permit free mobilization of the involved area may be desirable before surgical correction is instituted.

TABLE I—CONT'D

| SERIES NO. | HOSPITAL NO. | AGE | SIZE   | CAUSE                | NO. PREV. OPERATIONS | RESULT HERE | COMPLICATIONS       |
|------------|--------------|-----|--------|----------------------|----------------------|-------------|---------------------|
| 43         | 263386       | 36  | Medium | Plastic              | 0                    | +           | Pneumonia           |
| 44         | 474595       | 55  | Small  | Total hysterectomy   | 2                    | +           |                     |
| 45         | 484915       | 50  | Small  | Vaginal hysterectomy | 1                    | +           | Diabetes            |
| 46         | 484718       | 56  | Small  | Total hysterectomy   | 0                    | -           |                     |
| 47         | 489156       | 48  | Small  | Total hysterectomy   | 3                    | +           |                     |
| 48         | 479087       | 25  | Small  | Delivery             | 0                    | +           |                     |
| 49         | 479745       | 57  | Large  | Vaginal hysterectomy | 0                    | +           | Carcinoma of vagina |
| 50         | 492531       | 41  | Small  | Vaginal hysterectomy | 3                    | -           |                     |
| 51         | 478001       | 42  | Small  | Plastic              | 4                    | +           |                     |
|            |              |     |        |                      |                      |             | One kidney          |

membrane is then inverted into the bladder and the vaginal mucous membrane approximated in such a manner as to produce a minimum of tension. The many variations of this basic technique need not be discussed here. However, some of the more important details should be emphasized.

1. The fistula must be well visualized.

2. The tissues around the opening should be sufficiently mobilized to permit closure without tension. This mobilization may be achieved by adequate incision of scar tissue some time prior to operation or it may be accomplished at the time of operation. Since there is seldom extensive loss of tissue in the postoperative fistula, this mobilization is not only essential but generally possible.

3. Whether the suture lines are transverse or one above the other is in our experience a matter of little significance provided approximation be made in such a manner as to minimize tension.

4. Pale ragged, poorly vascularized edges of either bladder or vaginal mucous membrane should be excised.

5. In recent years much attention has been focused on suture material. Doubtless the various types of suture have their good points but so far as vesicovaginal fistulas are concerned our experience and the experience of others would seem to indicate that good results may be obtained with the use of either wire, silk, or fine catgut, provided, and this is important, excessive suturing is avoided and approximation, not strangulation be the function of each suture placed. We have used all three types of suture material but agree with Bertner<sup>8</sup> that fine catgut is as good as any.

6. It is unnecessary and sometimes harmful to produce a water and air tight wound. After all our prime task is to approximate raw surfaces without tension; nature and not our suturing brings about the actual healing. Purse-string sutures should be avoided.

## PARTIAL COLPOCLEISIS AS AN APPROACH TO VESICO-VAGINAL FISTULA FOLLOWING TOTAL HYSTERECTOMY\*

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IT IS significant to note the definite rise in the percentage of post-operative vesicovaginal fistulas as compared with the diminution of those complicating obstetric procedures. This reversal of ratio has become more apparent in the past two decades. It is attributable to the increased amount of pelvic surgery, both abdominal and vaginal, notably the more radical types of operations. The elimination of a cervix that is diseased and may be predisposed to malignant changes has served as the incentive for total abdominal as well as vaginal hysterectomy. The decline in the number of fistulas resulting from childbirth has been due to the advances made in obstetrics: namely, diminution of the hours of labor, better technique of forceps deliveries, and the relative safety of cesarean sections in dystocia.

The causative factors of the nonobstetric fistulas are:

A. Direct injury to the bladder† during operation, which is unrecognized. The importance of detecting bladder injury at the time of operation and a prompt repair by two to three layers of interrupted catgut sutures cannot be overemphasized.

B. Interference with the nerve and blood supply of the bladder, particularly in radical hysterectomy (abdominal or vaginal) for malignancy of the uterus.

C. Clamping or ligating a piece of the bladder in the closure of the vaginal vault, which later sloughs out, producing a fistula.

It must be borne in mind that these fistulas, following total hysterectomy are located high up in the vaginal vault, just above or on a level with the trigone and the ureteral openings. A brief anatomic consideration will enable one to visualize the reason for the location of these fistulas. There is approximately 1 cm. of bladder wall above the trigone which is in close connection to the anterior vaginal wall. The bladder injury usually occurs when the vagina is opened, amputated or sutured. The injury to the bladder therefore is generally near the trigone and in close proximity to the ureteral openings.

After total hysterectomy, the posterior and inferior margin of the bladder is in close contact with the sutured edge of the amputated

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†The instillation of methylene blue solution (1 to 2 per cent) into the bladder by an indwelling catheter has been employed to stain the bladder mucosa. This permits a greater ease in the prevention and recognition of bladder injuries.

3. The inverted Trendelenburg position and the vaginal approach is suitable for most postoperative fistulas.

4. In general the split flap (separation of bladder and vaginal mucous membrane) technique is desirable. Free undercutting to permit union without tension is essential.

5. Probably no one suture material justifies its sole use to the exclusion of others in the repair of vesicovaginal fistula.

6. Preoperative and postoperative use of stilbestrol in women past the menopause is desirable as a healing aid.

7. The use of catheter drainage for some days after operation is advocated.

8. The prone position for three or four days after operation is logical.

9. Patients with small fistulas may be up two to four days after operation without jeopardizing chances for cure.

10. A series of 51 vesicovaginal fistulas treated by me in the past ten years is reported.

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terminal portion of the greater omentum and sutured it between the vagina and the bladder. This prevented the sutured openings from coming in contact and also served as a re-enforcing patch. Danforth, in 1940, reported a similar success in a fistula occurring in a nullipara following total abdominal hysterectomy. The operative approach and technique was similar to that of Waters. The omentum in this case, however, could not be brought down to reach the desired area, and the operator therefore excised a portion of the omentum and placed it between the suture lines with fine catgut.

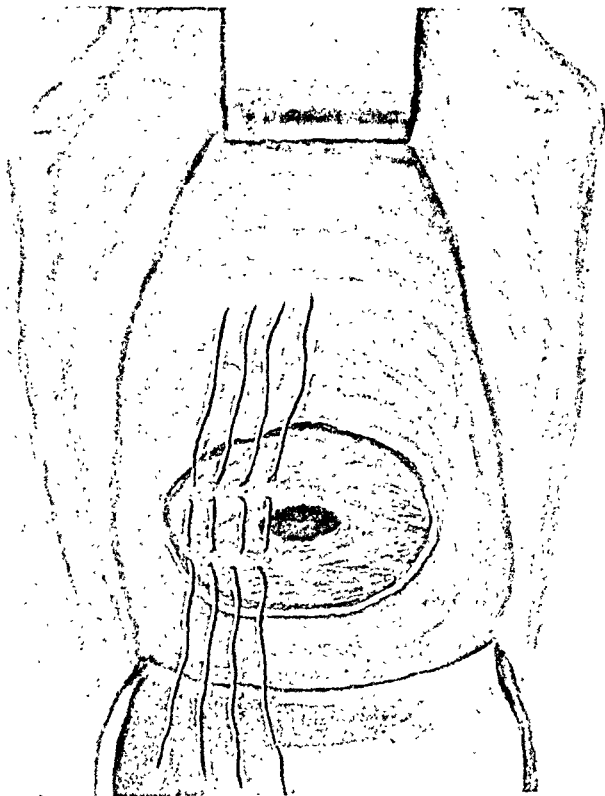


Fig. 1.—A circular area of mucous membrane has been denuded around the fistulous opening and the first four sutures have been placed.

Any of the above-mentioned operations may be attempted to cure a fistula of this type. However, it is a recognized fact that the vaginal approach to cure the fistula has no mortality, a minimal amount of shock, and offers fewer opportunities for complications than do the abdominal or transvesical approach. Being extraperitoneal, there is no danger of contamination of the peritoneum by the leakage of urine.

Partial colpocleisis, the Latzko operation (i.e., partial obliteration of the vagina), is offered as a treatment for vesicovaginal fistula. One rigid criterion exists: This operation should only be performed on fistulas resulting from *total* hysterectomy (abdominal or vaginal).

In this operation one makes use of the posterior vaginal wall as a transplant over the fistulous opening. The vaginal walls being con-

vagina, and they are both closely attached to the peritoneum. Since the absence of the uterus and cervix has eliminated the vesicouterine fold of peritoneum; any attempt at the classical method of mobilization of the bladder in this region is not only difficult due to its inaccessibility, but it fraught with considerable danger, for the peritoneum may be easily entered.

There are three methods of approach to such a fistula: transvesical, transperitoneal, or transvaginal.

The question of approach has become a subject of much controversy. Surgeons tend to favor the method of approach with which they are most familiar. Consequently, most urologists are exponents of the suprapubic transvesical operation which was first attempted by Trendelenburg in 1881. It was described in 1890 and was subsequently popularized in Europe. Exponents of this operation claim that there is no danger of opening and soiling the peritoneum. Moreover, the fistulous tract and the ureters are brought into direct view, thus minimizing injury to the latter. If any question arises as to the patency and configuration of the ureters, a catheter may be inserted and the ureters outlined. Various methods have been used to elevate the fistula into the bladder and make it more accessible for dissection: (a) packing the vagina and putting a hook in the packing so as to elevate the fistula (b) the use of a hook or a perineal prostatic retractor. This extraperitoneal transvesical approach has been recommended for high, small, inaccessible fistulas, closely allied to the ureteral orifices away from the bladder neck. It has also been advocated for the repair of fistulas associated with the absence of the uterus and the cervix. I. Farsht has reported seventeen cases cured by the transvesical repair. One-half had been caused by obstetric complications, the other half by previous surgical procedures. Douglass also described four postoperative gynecologic fistulas cured by this approach.

The transperitoneal approach has been extensively employed by Legeue. From 1914 to 1929 he reported 24 cases cured and one death following this procedure. A longitudinal incision is made through the peritoneum on the posterior bladder wall. The bladder is mobilized. The vaginal and bladder sides of the fistula are separated and closed independently with catgut sutures. The suture lines are kept apart and the peritoneum is approximated with fine chromic catgut. Koster, too, has employed the transperitoneal approach and claims good results. He states that peritoneal soiling with urine is minimal.

All authors have emphasized the need of keeping the suture lines apart and, if feasible, of maintaining them in different planes. A new concept for the separation of the two suture lines was introduced in 1937 by W. Waters. During a repair for a recurrent vesicovaginal fistula by means of the transperitoneal approach, he brought down the

Furthermore, the protracted need for postoperative indwelling catheters has not been found necessary. It should be left in for forty-eight hours and should then be removed and the patient should attempt to void. With the constant flow of urine into the bladder from the ureters, it is impossible to keep the bladder dry even with an indwelling catheter.

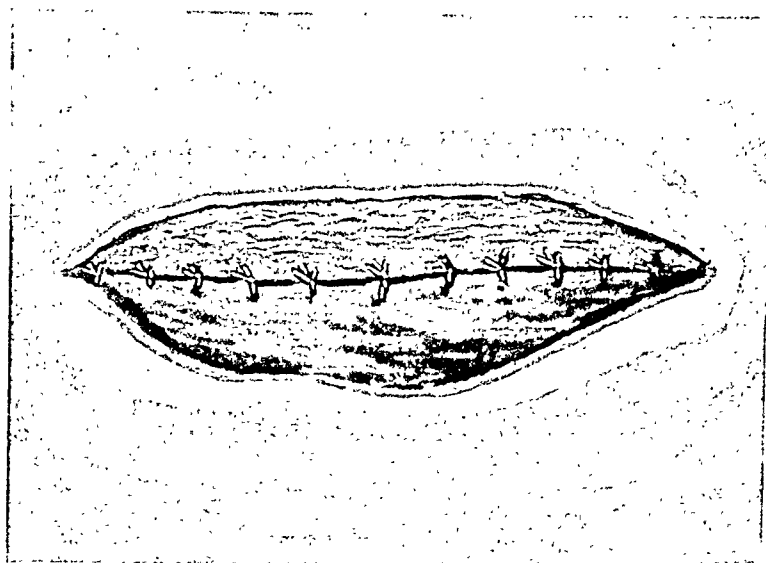


Fig. 3.—First layer of sutures have been tied.

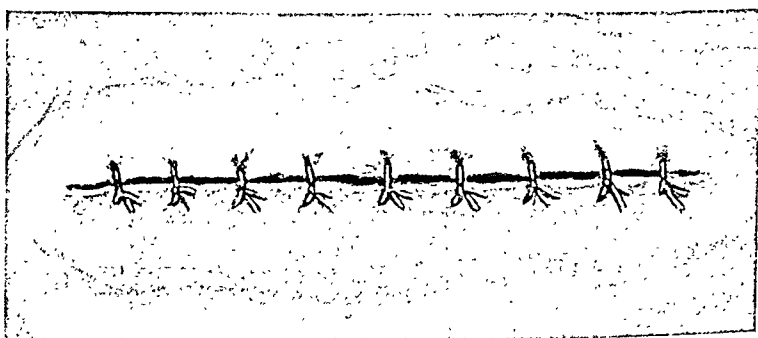


Fig. 4.—The top layer of sutures have been tied. The operation is now completed.

Catheterization should be performed every two to four hours and the time gradually lengthened until the patient can void voluntarily. Overdistention of the bladder need not be feared as it cannot cause any tension on the suture line. Small doses of sulfathiazole, 0.5 Gm. q. 4 h., serves as an excellent urinary antiseptic while catheterization is necessary. These patients are comfortable and move about freely in bed. The postoperative nursing care is similar to any vaginal plastic operation.

#### RESULTS

My associate, Dr. Henry C. Falk and I have performed this operation on four cases, each being successful. I had failed previously to cure one of these cases by the suprapubic transvesical route.

stantly in contact lend themselves readily to this procedure, placing no tension on any of the suture lines.

#### TECHNIQUE

A circular area of mucous membrane 1.5 cm. in diameter is denuded around the fistulous opening; all the vaginal mucosa up to and including the fistulous edge is removed in this area. The fistula is always found on the anterior vaginal wall. The denuded area on the anterior vaginal wall is sutured to the denuded area on the posterior wall in 3 layers, using fine chromic catgut.

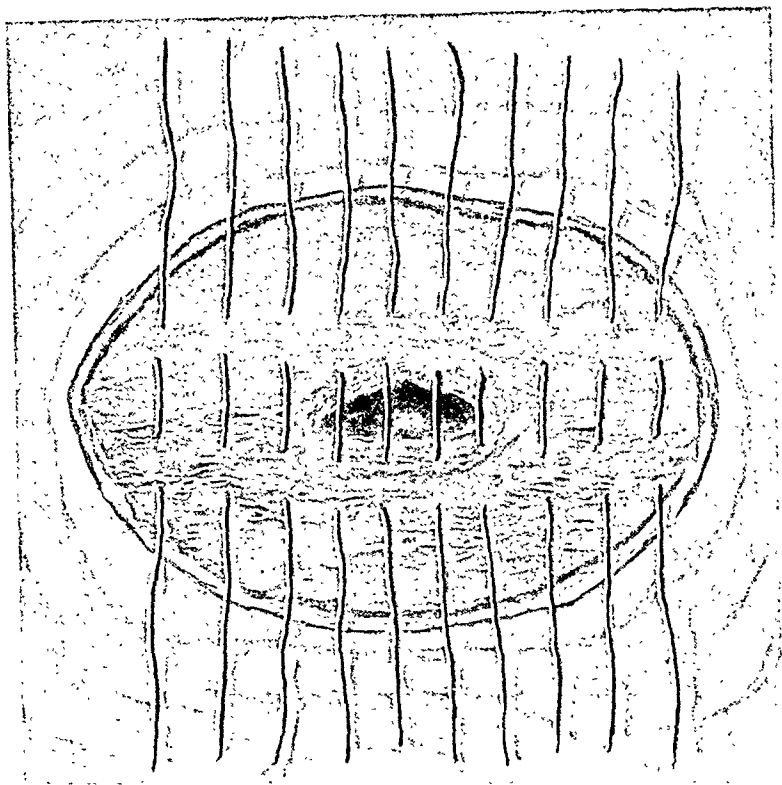


Fig. 2.—The fistulous opening with the denuded circular area around it and the first layer of sutures in place.

If the vagina is nulliparous and tubular, the opening may be enlarged by a simple episiotomy or if more room is necessary, a Schuchardt incision may be used. If the opening is ample but the fistula inaccessible, it can be brought into the wound by using hooks or a Young's perineal retractor.

Most authors stress the need for exacting pre- and postoperative care if successful results are to be obtained. This includes preoperative cystoscopic examination, intravenous urography, and a knowledge of the relationship between the fistula and the ureters. Postoperatively, nearly all surgeons advocate some form of indwelling catheter for two to three weeks in an attempt to keep the bladder free from urine. Some form of urinary antiseptic is likewise employed.

Since mobilization is not needed, the necessity of inserting ureteral catheters and the hazard of injuring the ureters are practically eliminated.



In performing total hysterectomy two things are essential: an observance of the indications for and against the operation, and proper operative technique. We have never had a vesicovaginal fistula in any case in which the Richardson technique of total abdominal hysterectomy was employed.

Dr. Miller mentioned the desirability of cystoscopy and of determining the relation of the ureteral orifices to the fistula. He also spoke of the difficulties in filling the leaking bladder with water. It seems to me the best answer to this is air cystoscopy in the knee-elbow posture in which procedure one can always get property dilatation of the bladder regardless of the size of the opening. Even in the high fistulas following total hysterectomy I agree with both the essayists that the best approach is almost always through the vagina. I have never seen a case in which I felt the transvesical approach, as advocated by some urologists, was indicated. Occasionally, the transperitoneal approach is the easiest. After separation of the bladder and vagina and closure of the fistula, one can sometimes bring down a flap of peritoneum over the closed opening in the bladder and thus reinforce the closure.

I agree that fine catgut is, in general, the most satisfactory suture material but in difficult large fistulas silver wire has the advantage that it can be left in for as long as fourteen days without infection. It should only be used for approximating the vaginal mucosa and not through the bladder mucosa. This is true of any nonabsorbable suture material which may cut through the vaginal mucosa and be lost on the bladder side of the closure, where it will invariably form a calculus. We have had two such cases sent to us in the past year, one due to silver wire and one due to silk.

One of the most important steps in the cure of the fistula is the postoperative care. Many a good surgical procedure has been ruined by permitting the bladder to become distended. With this possibility in mind I have recently, in very difficult cases, provided for a double safety valve in the form of an indwelling urethral catheter and suprapubic drainage. I am certain that this double outlet has prevented a few failures for us. The suprapubic tube drains very well with the patient lying on her side. I do not feel that the uncomfortable prone position is necessary. The clear uninfected urine does not retard healing, provided there is no pressure from distention. Another procedure, which I have occasionally used since it was demonstrated to me by Dr. Hunner several years ago, is to make another fistula with a clean cut of the scalpel in front of or behind the closed fistula and leave a catheter in it. Such fistulas almost always close spontaneously and promptly.

Dr. Holden's idea of closure of high postoperative fistulas, by approximation of the anterior and posterior vaginal walls, will, I believe, make many a difficult closure easy. I can see one disadvantage in it, however, in young women for there will be a little shortening of the vagina which may have already been somewhat shortened by the total hysterectomy. We have, on rare occasions, completely closed the vagina as in the following case. Huge recto- and vesicovaginal fistulas appeared twelve years after radium for cervical carcinoma. Closure of either seemed quite out of the question. We first performed a permanent sigmoidostomy and later closed the vagina entirely. The patient now defecates into a colostomy cup, voids through the rectum, and is quite happy.

DR. JAMES R. MILLER, HARTFORD, CONN.—I would like to report a recent case which presents somewhat different principles. A patient, 22 years of age, who had had a panhysterectomy for stroma cell endometriosis, came for the closure of a fistula three months after her original operation. She had a very small introitus and a liberal Schuchardt incision had to be made. There was found a loss of the upper third of the trigone with the right urethral orifice on the edge of the fistula. I circumcised the top of the vagina, mobilizing the vaginal tissue and

It is not necessary that the interval be long after the injury to do this operation.

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## DISCUSSION ON PAPERS BY DR. N. F. MILLER AND DR. F. C. HOLDEN

DR. LOUIS E. PHANEUF, BOSTON, MASS.—I have operated upon 23 women for vesicovaginal fistulas. Five of these had obstetric fistulas, consequent to vaginal cesarean section in one patient, to forceps extraction in 2 patients, and to version and extraction in 2 patients. Eighteen had surgical fistulas, which followed the interposition operation in one patient, vaginal hysterectomy in one patient, abdominal panhysterectomy in 7 patients, abdominal supravaginal hysterectomy in 3 patients, vaginal trachelectomy subsequent to abdominal supravaginal hysterectomy in 1 patient, the Manchester or Fothergill operation in 1 patient, amputation of the cervix in 1 patient, anterior colporrhaphy in 2 patients, and the Kennedy operation for incontinence of urine in 1 patient.

The smallest number of operations required to close the fistulas was 1, and the largest 7, the majority of these patients having had numerous attempts at closure before being referred to me. In Case 23 the fistula followed an anterior colporrhaphy performed by a general practitioner, who operated six times without success. I was finally successful in closing the fistula at the seventh operation.

The following procedures were employed at the final operation in these 23 women: extraperitoneal closure through a Pfannenstiel incision and implantation of the right ureter in the bladder in one patient; transplantation of the ureters in the sigmoid in 3 patients; vaginal closure in 17 patients; and colpocleisis in 2 patients. Twenty-two women were cured. The twenty-third had shown a satisfactory result at two examinations after operation, but two weeks ago a pinpoint opening was discovered which still may close spontaneously.

The technique which has served me best in the vaginal closure of 17 of these fistulas, some of which were surrounded by dense scar tissue from previous operations, has consisted of free mobilization of the bladder from the anterior vaginal wall, of approximating the edges of the bladder with fine chromic catgut, of avoiding the bladder mucosa, and of uniting the edges of the anterior vaginal wall with silver wire, which for the past seven years has been replaced by rustless alloy steel wire as recommended by Dr. W. Wayne Babcock. I have succeeded by this method, after failure had occurred in the hands of others who had used catgut sutures throughout. The metallic sutures are removed at the end of a month, under intravenous or general anesthesia, in order to permit relaxation of the patient during the intervention.

For the last two decades it has become evident to me that the obstetric fistulas have been decreasing, because of better obstetrics, while the opposite trend obtained with surgical fistulas, due to the increasing number of operative procedures on the female pelvic organs.

DR. RICHARD W. TELINDE, BALTIMORE, MD.—These papers are very timely, for they both indicate that the increased popularity of total hysterectomy has brought with it an increased incidence of postoperative vesicovaginal fistulas. Our own experience coincides with theirs. In the past year I have operated upon 5 vesicovaginal fistulas, only one of which was the result of obstetrics, while 4 were postoperative. Among the latter, three followed total abdominal hysterectomy and 1 followed a cesarean section.

# MORPHINE SULFATE AS AN OBSTETRIC ANALGESIC\*

## A CLINICAL ANALYSIS

WILLIAM F. MENGERT, M.D., IOWA CITY, IOWA

*(From the Department of Obstetrics and Gynecology, The State University of Iowa)*

IT HAS long been common knowledge that clinically normal babies are sometimes born after the administration of enormous total doses of morphine to patients with toxemia of pregnancy. In one such instance, the child lived and prospered following the administration of 2 gr. of morphine to the mother during the twenty-two hours preceding birth. Similar instances, but with smaller total doses, have been observed with sufficient frequency to prompt an inquiry into the actual and potential dangers of the use of the drug as an obstetric analgesic.

### METHOD

Beginning in March, 1941, a record was made on a punch card (Fig. 1) immediately after each labor of: the type, quantity and timing of the analgesic drug, the type and duration of the anesthetic, various maternal complicating factors, the time at which extrauterine, spontaneous breathing began or the nature of the various resuscitative measures which were instituted and the type of labor. Later the subsequent course of the child was added to the record. The onset of spontaneous breathing, although timed and recorded in fifteen-second periods, was analyzed in two thirty-second intervals. The condition of the child at birth was classified into 4 groups: respiratory distress, as evidenced by apnea after spontaneous breathing or cyanosis, paleness, limpness, and circulatory distress including slow, weak, and irregular pulse. The common resuscitative measures included clearing of air passages with a soft rubber bulb syringe, administration of oxygen, surface friction, immersion in warm water, and the introduction of a catheter into the trachea. Analeptics were seldom, if ever, employed. Breast feeding of all babies was encouraged so that the percentage of breast-fed babies represents to some extent a measure of the normality of the course of the child. Since our obstetric patients are commonly discharged on the ninth post-partum day, the infants do not remain in the hospital a sufficient length of time to warrant using the recapture of the birth weight as an index of their hospital course.

Because this study was directed primarily at achieving a clinical evaluation of morphine sulfate when employed as an obstetric analgesic, the general use of the drug was encouraged, but in practice 60 per cent of the patients receiving it were primigravidas.

\*Presented, by invitation, at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.

utilizing it in the closure of the fistula. Now she has a "blowout patch" of vaginal squamous cell epithelium in the wall of the bladder. It is now twenty-nine days since the operation and the fistula has remained closed. It is my purpose in a few months to treat her with stilbestrol and see if it is possible to evoke a reaction from this dislocated tissue.

DR. N. SPROAT HEANEY, CHICAGO, ILL.—Some years ago I had an interesting experience with a patient who had had an abdominal hysterectomy for carcinoma of the cervix. A recurrence developed in the vaginal vault and one day when her bladder filled up it burst. The recurrence was treated with radium and I was surprised to find that between each application of radium the bladder healed shut. In several cases since that time where there has been a very small vesicovaginal fistula, the size of silkworm gut, I have introduced into the tract a radium needle of 12.5 mg. and have left it in for eighteen to twenty hours. In a number of cases I have had only one case that refused to heal. With this therapy an edema causes the fistula to close for several days with immediate continence. Later it may leak and then close finally after a period of ten to twelve days.

DR. W. LATZKO, NEW YORK, CITY, N. Y.—I would like to refer to 3 cases to show the great difference between the results of Simon's "high occlusion" of the vagina and my procedure, which ought to be called "obliteration of the vaginal vault."

The first patient had a large vesicovaginal fistula closed indirectly by high occlusion, with the formation of a deep diverticulum. The borders of the diverticulum are identical with those of the original fistula. The inferior border is formed by the interureteric ligament and shows the orifice of the right ureter.

In Case 2 the fistula was closed according to my method. No diverticulum is formed but instead of it there is a flat, white scar which terminates in a small niche.

An enormous fistula was found in the third case. The fundus of the bladder and the trigone were destroyed. All that remained was the interureteric ligament which run as a string through the field. The white scar behind the interureteric ligament passed into the hyperemic remainder of the posterior wall of the bladder. The avoidance of the formation of a diverticulum is an obvious advantage of my procedure of obliteration of the vaginal vault.

I have operated upon 31 postoperative vesicovaginal fistulas, most of them having arisen after abdominal radical operations for uterine cancer. All were closed in the indirect manner. The results included one failure by a technical mistake; one improvement to the full satisfaction of the patient, who renounced a further operation. The remaining 29 cases were all perfectly cured by a simple operation.

DR. HOLDEN (closing).—Dr. TeLinde's remark in regard to shortening the vagina is very appropriate. In a shallow vagina we put only two layers of sutures. With a deeper vagina we feel that it is better to use the three layers of sutures.

were always performed with the patient under the influence of some other appropriate medium.

On the other hand various types of inhalation and block anesthetics, selected according to existing exigencies, were administered during the second stage of labor to the 807 women of the group receiving analgesia during the first stage. The types and combinations employed are listed in Table III. In general, patients requiring obstetric operations received cyclopropane.

TABLE I. ANALGESICS EMPLOYED IN ORDER OF FREQUENCY

|   |     |
|---|-----|
| 1. Morphine alone                                     | 217 |
| 2. Morphine and scopolamine                           | 161 |
| 3. Sodium pentobarbital                               | 135 |
| 4. Morphine, scopolamine, and sodium pentobarbital    | 85  |
| 5. Morphine and sodium pentobarbital                  | 64  |
| 6. Scopolamine alone                                  | 36  |
| 7. Sodium pentobarbital and scopolamine               | 35  |
| 8. Morphine and miscellaneous<br>(not included above) | 28  |
| 9. Sodium amytal alone                                | 22  |
| 10. Rectal ether                                      | 17  |
| 11. Miscellaneous<br>(not included above)             | 7   |
| Total   | 807 |
| Total receiving morphine alone and in combination     | 564 |
| Total receiving all other drugs                       | 243 |

TABLE II. QUANTITY OF THREE MOST COMMONLY EMPLOYED ANALGESIC DRUGS

| MORPHINE       |                   |                   | SCOPOLAMINE      |                   |                   | SODIUM PENTOBARBITAL |                   |                   |
|----------------|-------------------|-------------------|------------------|-------------------|-------------------|----------------------|-------------------|-------------------|
| GRAINS         | PRIMI-<br>GRAVIDA | MULTI-<br>GRAVIDA | GRAINS           | PRIMI-<br>GRAVIDA | MULTI-<br>GRAVIDA | GRAINS               | PRIMI-<br>GRAVIDA | MULTI-<br>GRAVIDA |
| $\frac{1}{8}$  | 14                | 14                | $\frac{2}{600}$  | 2                 | 4                 | $\frac{3}{4}$        | 0                 | 0                 |
| $\frac{1}{6}$  | 90                | 80                | $\frac{3}{600}$  | 43                | 48                | $1\frac{1}{2}$       | 30                | 14                |
| $\frac{1}{4}$  | 68                | 67                | $\frac{4}{600}$  | 75                | 68                | 3                    | 60                | 94                |
| $\frac{1}{3}$  | 40                | 5                 | $\frac{5}{600}$  | 1                 | 1                 | $4\frac{1}{2}$       | 16                | 60                |
| $\frac{3}{8}$  | 23                | 8                 | $\frac{6}{600}$  | 8                 | 5                 | 6                    | 13                | 5                 |
| $\frac{1}{2}$  | 47                | 4                 | $\frac{7}{600}$  | 6                 | 4                 | $7\frac{1}{2}$       | 5                 | 5                 |
| $\frac{5}{8}$  | 2                 | 0                 | $\frac{8}{600}$  | 8                 | 0                 | 9                    | 2                 | 0                 |
| $\frac{3}{4}$  | 6                 | 1                 | $\frac{9}{600}$  | 0                 | 0                 | $10\frac{1}{2}$      | 0                 | 1                 |
| 1              | 2                 | 0                 | $\frac{10}{600}$ | 4                 | 1                 |                      |                   |                   |
| $1\frac{1}{4}$ | 1                 | 0                 | $\frac{11}{600}$ | 3                 | 0                 |                      |                   |                   |
|                |                   |                   | $\frac{12}{600}$ | 0                 | 0                 |                      |                   |                   |
|                |                   |                   | $\frac{13}{600}$ | 1                 | 0                 |                      |                   |                   |
| Totals         | 293               | 179               |                  | 151               | 131               |                      | 126               | 179               |

Records of all patients with premature babies, pregnancy complications, and fetal death clearly not due to the analgesic medium were excluded.

TABLE III. ANESTHETICS AMONG 807 WOMEN RECEIVING FIRST STAGE ANALGESICS (ORDER OF FREQUENCY)

|   |     |
|---|-----|
| 1. Chloroform, alone and in combination   | 343 |
| 2. Cyclopropane, alone and in combination | 289 |
| 3. Nitrous oxide, alone or with ether     | 90  |
| 4. Block anesthesia                       | 43  |
| 5. Ether alone                            | 8   |
| 6. None                                   | 34  |

## PATIENTS

Among a consecutive series of 1,534 parturient women, analgesic drugs of various kinds and combinations were administered to 807, of whom 386 were primigravidas.

Seven hundred and twenty-seven women received no analgesic drug and served as controls. However, only a very few (58) of these patients were primigravidas, a fact which was considered in evaluation and comparison.

## ANALGESIC DRUGS

There is no routine obstetric analgesic in the Iowa clinic and the chief concern is individualized medication. The kinds and combinations of analgesic drugs employed in the 807 women of this study are shown in Table I and the quantities of morphine, scopolamine, and sodium pentobarbital administered to essentially normal patients in Table II.

|  |  |             |  |             |  |              |  |              |  |                |  |                |  |                                  |  |      |  |             |  |               |  |               |  |               |  |                |  |                   |  |              |  |        |  |      |  |             |  |              |  |              |  |            |  |             |  |               |  |              |  |               |  |             |  |  |  |                         |  |  |  |  |  |  |  |  |  |  |  |  |  |
|--|--|-------------|--|-------------|--|--------------|--|--------------|--|----------------|--|----------------|--|----------------------------------|--|------|--|-------------|--|---------------|--|---------------|--|---------------|--|----------------|--|-------------------|--|--------------|--|--------|--|------|--|-------------|--|--------------|--|--------------|--|------------|--|-------------|--|---------------|--|--------------|--|---------------|--|-------------|--|--|--|-------------------------|--|--|--|--|--|--|--|--|--|--|--|--|--|
| MORPHINE   |  | HEM<br>SUTL |  | SEC<br>DIAL |  | ADD<br>ANTHL |  | DPO<br>ADIAL |  | PAREL<br>DINTL |  | ESTAL<br>ESTAL |  | OTHER                            |  | NONE |  | NTR<br>DICE |  | CHLO<br>DIPUM |  | CYPR<br>DIPUM |  | CHLO<br>DIPUM |  | PAREL<br>DINTL |  | CAL<br>DIAL       |  | PARA<br>DIAL |  | SPIRAL |  | NONE |  | DPO<br>DIAL |  | 21-40<br>min |  | 11-40<br>min |  | PLUS<br>60 |  | TOX<br>EMIA |  | PAREL<br>PREV |  | PRISM<br>SEP |  | PRISM<br>ATRE |  | DAY<br>VITK |  |  |  |                         |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ANALGESIC  |  |             |  |             |  |              |  |              |  |                |  |                |  | ANESTHETIC                       |  |      |  |             |  |               |  |               |  |               |  |                |  | DURATION          |  |              |  |        |  |      |  |             |  |              |  |              |  | INHALATION |  |             |  |               |  |              |  |               |  |             |  |  |  | ANTEPARTUM COMPLICATION |  |  |  |  |  |  |  |  |  |  |  |  |  |
| NAME <u>Doe, Janet</u>                                   |  |             |  |             |  |              |  |              |  |                |  |                |  | DOSE                             |  |      |  |             |  |               |  |               |  |               |  |                |  | ANALGESIA         |  |              |  |        |  |      |  |             |  |              |  |              |  | TIME GIVEN |  |             |  |               |  |              |  |               |  |             |  |  |  | DATE                    |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hosp. number <u>XX</u> Gravidia <u>1</u>                 |  |             |  |             |  |              |  |              |  |                |  |                |  | 1 <u>Morphine</u> <u>gr 1/4</u>  |  |      |  |             |  |               |  |               |  |               |  |                |  | 2 <u>11:30 AM</u> |  |              |  |        |  |      |  |             |  |              |  |              |  | 7.10.41    |  |             |  |               |  |              |  |               |  |             |  |  |  |                         |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Age <u>19</u> Para <u>0</u>                              |  |             |  |             |  |              |  |              |  |                |  |                |  | 3                                |  |      |  |             |  |               |  |               |  |               |  |                |  |                   |  |              |  |        |  |      |  |             |  |              |  |              |  |            |  |             |  |               |  |              |  |               |  |             |  |  |  |                         |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Delivery, Date <u>7.10.41</u> Time <u>5:30 pm</u>        |  |             |  |             |  |              |  |              |  |                |  |                |  | 4                                |  |      |  |             |  |               |  |               |  |               |  |                |  |                   |  |              |  |        |  |      |  |             |  |              |  |              |  |            |  |             |  |               |  |              |  |               |  |             |  |  |  |                         |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Labor, Duration <u>12 hr 39 min</u> 1st St. <u>11-15</u> |  |             |  |             |  |              |  |              |  |                |  |                |  | 5                                |  |      |  |             |  |               |  |               |  |               |  |                |  |                   |  |              |  |        |  |      |  |             |  |              |  |              |  |            |  |             |  |               |  |              |  |               |  |             |  |  |  |                         |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 2nd St. <u>1-16</u>                                      |  |             |  |             |  |              |  |              |  |                |  |                |  | 6                                |  |      |  |             |  |               |  |               |  |               |  |                |  |                   |  |              |  |        |  |      |  |             |  |              |  |              |  |            |  |             |  |               |  |              |  |               |  |             |  |  |  |                         |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hosp. Baby, number <u>XX</u> Weight <u>3200 gms.</u>     |  |             |  |             |  |              |  |              |  |                |  |                |  | 7                                |  |      |  |             |  |               |  |               |  |               |  |                |  |                   |  |              |  |        |  |      |  |             |  |              |  |              |  |            |  |             |  |               |  |              |  |               |  |             |  |  |  |                         |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Abnormalities <u>none</u>                                |  |             |  |             |  |              |  |              |  |                |  |                |  |                                  |  |      |  |             |  |               |  |               |  |               |  |                |  |                   |  |              |  |        |  |      |  |             |  |              |  |              |  |            |  |             |  |               |  |              |  |               |  |             |  |  |  |                         |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Continue on reverse side, if necessary                   |  |             |  |             |  |              |  |              |  |                |  |                |  | Signature <u>John Smith M.D.</u> |  |      |  |             |  |               |  |               |  |               |  |                |  |                   |  |              |  |        |  |      |  |             |  |              |  |              |  |            |  |             |  |               |  |              |  |               |  |             |  |  |  |                         |  |  |  |  |  |  |  |  |  |  |  |  |  |

Chart 1.—A typical card.

During analysis of the data, certain clinic tendencies became manifest. Morphine was not only given more freely to primigravidas than to multigravidas, but also was employed in the presence of complicated labors in general, and toxemia and prolonged labor in particular. Analgesics other than morphine were employed among multigravidas 4 times more often than in primigravidas. Scopolamine was seldom used alone. Although more than 300 patients received the drug, only 36 had no other.

## ANESTHETIC DRUGS

Since the group of 727 patients receiving no analgesia represents a natural selection of essentially normal multiparas, the type of second stage medication was quite distinct from the other group. Thus, the average normal multipara with no premedication tended to receive chloroform as an analgesic drug intermittently with the pains. It is emphasized that chloroform was never used to produce complete unconsciousness. Obstetric procedures necessitating surgical anesthesia

Despite the exclusions previously made, the feeling persisted that comparable series had not been obtained. The group receiving no analgesia was composed almost entirely of multigravidas, while the majority of the patients in the morphine group were primigravidas. A final subdivision of the groups into primigravidas and multigravidas was, therefore, made and tabulated (Table VI). Morphine still seems to be a more dangerous drug than sodium pentobarbital. However, the differences are not so marked, especially in the comparisons among the multigravidas. In fact, in the latter group, the principal point of difference seems to be in the greater percentage of respiratory difficulties, which included mild cyanosis and apnea following spontaneous respiration.

TABLE V. COMPARISON OF GROUPS RECEIVING NO ANALGESIA, MORPHINE ALONE AND SODIUM PENTOBARBITAL ALONE (STANDARD EXCLUSIONS)

(FIGURES REPRESENT PERCENTAGES)

|                                       |                        | NO<br>ANALGESIA | MORPHINE<br>ALONE | SODIUM<br>PENTO-<br>BARBITAL<br>ALONE |
|---------------------------------------|------------------------|-----------------|-------------------|---------------------------------------|
| PATIENTS, NUMBER                      |                        | 666             | 172               | 127                                   |
| Spontaneous breathing                 | 1-30 sec.              | 96.7            | 84.9              | 90.4                                  |
|                                       | 31-60 sec.             | 1.8             | 9.3               | 7.1                                   |
| Fetal distress immediately post natal | Respiratory            | 3.6             | 24.4              | 14.2                                  |
|                                       | Pale                   | 0.8             | 1.7               | 2.4                                   |
|                                       | Limp                   | 0.3             | 6.9               | 4.7                                   |
|                                       | Circulatory            | 0.0             | 2.3               | 3.2                                   |
| Resuscitative measures                | Bulb                   | 8.1             | 15.1              | 11.0                                  |
|                                       | Friction               | 17.3            | 23.3              | 14.9                                  |
|                                       | O <sub>2</sub>         | 0.9             | 12.2              | 5.5                                   |
|                                       | Tub                    | 0.8             | 12.2              | 5.5                                   |
|                                       | Intratracheal catheter | 0.8             | 4.1               | 3.2                                   |
| Breast feeding                        |                        | 79.9            | 55.2              | 77.9                                  |
| Stillbirth and neonatal death         |                        | 0.9             | 1.7               | 0.8                                   |
| Labor                                 | Spontaneous            | 95.3            | 80.8              | 89.7                                  |
|                                       | Low forceps            | 1.1             | 16.3              | 6.3                                   |
|                                       | Other operations       | 3.3             | 2.9               | 3.9                                   |

By the time so many "breakdowns" have been made, the series becomes too small to be of great significance. Nevertheless, it is felt that only by such limitation of extraneous factors is it possible to attain true comparisons. Many papers extolling the virtues of this or that analgesic medium or technique have failed to consider all the factors involved.

A final analysis concerning the fetal effects of morphine in relation to the time interval before delivery was made (Table VI). In general the results agree with those obtained by Shute and Davis,<sup>1</sup> namely, that administration of morphine during the third and second hours preceding delivery is attended by the highest percentage of fetal difficulties. During the first hour, and after the third or fourth hour, the effects of the drug on the fetus are minimal.

Also analyzed, but not presented in tabular form, was the effect of morphine on 22 immature infants weighing between 1,500 and 2,499 Gm. More than one-third of them exhibited respiratory distress at birth, and nearly one-third ultimately died.

## RESULTS

A gross comparison among all patients receiving no analgesia, those with morphine alone or in combination, and those with all other analgesic drugs (Table IV) seems to indicate that morphine, alone and in combination, was associated with the highest percentage of respiratory and circulatory difficulties at birth and of fetal death. Moreover, the percentage of low forceps operations in the morphine group was 3 times higher than among the patients receiving other analgesics and 9 times greater than in the control group. Since too many extraneous factors are introduced by study of *combinations* of other drugs with morphine, or in fact by study of any set of combinations, series of patients receiving single drugs were analyzed. Consideration of the 217 patients who received no analgesic other than morphine, however, did not appreciably alter the figures. Since morphine tended to be employed in the unusual type of patient, it was decided to make certain standard exclusions throughout the remainder of the analyses. These included: all cases where the infant weighed less than 2,500 Gm. at birth, all cases with ante-partum maternal complicating factors, such as placenta previa, abruptio placentae, severe maternal toxemia, and all stillbirths and neonatal deaths at term where the fatality was clearly due to some proved factor other than analgesia, such as macerated fetuses, death associated with diabetes, eclampsia, ruptured uterus, craniotomy, and erythroblastosis. Where no such well-defined and definite entity existed, fetal fatalities were included.

TABLE IV. COMPARISON OF INFANTS RECEIVING NO ANALGESIA, MORPHINE ALONE AND IN COMBINATION, AND ALL OTHER ANALGESICS

(FIGURES REPRESENT PERCENTAGES)

|                                      |                        | NO<br>ANALGESIA | MORPHINE | ALL OTHER<br>ANALGESICS |
|--------------------------------------|------------------------|-----------------|----------|-------------------------|
| PATIENTS, NUMBER                     |                        | 727             | 564      | 243                     |
| Spontaneous breathing                | 1-30 sec.              | 95.5            | 79.6     | 91.4                    |
|                                      | 31-60 sec.             | 1.9             | 10.8     | 5.8                     |
| Fetal distress immediately postnatal | Respiratory            | 4.3             | 26.3     | 15.6                    |
|                                      | Pale                   | 1.1             | 4.1      | 0.4                     |
|                                      | Limp                   | 0.7             | 9.0      | 4.1                     |
|                                      | Circulatory            | 0.4             | 7.9      | 2.5                     |
| Resuscitative measures               | Bulb                   | 7.7             | 18.5     | 10.7                    |
|                                      | Friction               | 17.2            | 34.1     | 14.8                    |
|                                      | O <sub>2</sub>         | 1.4             | 15.6     | 5.4                     |
|                                      | Tub                    | 1.4             | 17.6     | 6.6                     |
|                                      | Intratracheal catheter | 1.1             | 6.6      | 3.5                     |
| Breast feeding                       |                        | 73.5            | 66.0     | 74.2                    |
| Stillbirth and neonatal death        |                        | 2.3             | 5.9      | 2.9                     |
| Labor                                | Spontaneous            | 94.5            | 75.2     | 90.9                    |
|                                      | Low forceps            | 1.9             | 17.9     | 5.4                     |
|                                      | Other operations       | 3.9             | 6.4      | 3.7                     |

Table V compares 3 series: no analgesia, morphine alone, and sodium pentobarbital alone, after such standard exclusions. The discrepancies among these groups are not so large as in the previous table. Nevertheless, the use of morphine still appears to be attended with considerable respiratory embarrassment, some interference with breast feeding, too many fetal deaths, and too many low forceps operations.



## DISCUSSION

It is generally recognized that morphine stands supreme as an analgesic drug. Therefore, its use in labor is indeed rational, if the attendant dangers are not too great. On the other hand the drugs usually employed in reasonable dosages during labor generally produce amnesia rather than analgesia. Because morphine is admittedly a respiratory depressant, most obstetricians use it with caution, if at all. There are, however, others who feel that the fetal dangers resulting from the employment of morphine during the first stage of labor have been exaggerated. Such figures as have been obtained seem to indicate that morphine is not without danger to the fetus, although those dangers are not so excessive as generally believed. One is inclined to agree with Cole, Kimball, and Daniels<sup>2</sup> that "all sedative drugs increase the incidence of asphyxia" and the danger to the fetus "in direct proportion to the amounts used."

Since morphine is not without effect on the fetus, it is of interest to understand how the effect is produced. Snyder and Lim<sup>3</sup> have shown that rhythmical breathing of rabbit fetuses observed within the unopened uterus in a bath of warm Ringer's solution persisted despite administration to the mother of more than 15 times the analgesic dose of morphine. In another publication,<sup>4</sup> these authors report the effect of morphine on labor following delivery of rabbit fetuses from heavily morphinized mothers in two ways, hysterotomy and spontaneous labor. "In striking contrast to delivery by hysterotomy the incidence of stillbirths amounted to 70 per cent when the birth occurred spontaneously." They feel that the "chief damage of morphine is on the labor mechanism rather than directly on the fetus." Such an interpretation would explain the high percentage of respiratory difficulties and fetal death following morphine administration to the mothers of 22 premature infants where admittedly the trauma of labor is relatively severe.

Unquestionably, many factors combine to determine the effect of the drug upon the newborn infant. Two have been mentioned, the timing of the administration in relation to delivery, and the trauma of labor. Other factors include the size of the dose, the anesthetic and accessory drugs. Morphine in therapeutic doses probably does not exert a deleterious effect upon the fetus in utero. In other words, a pregnant woman may be given morphine without stint and without fear for her child. It is only when the drug is administered to parturient women, and then within two to three hours of delivery, that respiratory embarrassment may be anticipated. Even so, Shute and Davis<sup>1</sup> point out, "It is interesting to note that a large number of infants born under optimum conditions for the production of narcosis showed no trace of the effects of the drug." As an example, an infant of the present series breathed and cried immediately, and showed no sign of any difficulty after the hypodermic injection to the mother of  $\frac{1}{2}$  gr. of morphine two

TABLE VI. COMPARISON OF GROUPS RECEIVING NO ANALGESIA, MORPHINE ALONE AND SODIUM PENTOBARBITAL ALONE (STANDARD EXCLUSIONS)

|                                       |                        | PRIMIGRAVIDAS |                        |                            | MULTIGRAVIDAS |                        |                            |
|---------------------------------------|------------------------|---------------|------------------------|----------------------------|---------------|------------------------|----------------------------|
|                                       |                        | NO ANALGESIA  | MORPHINE SULFATE ALONE | SODIUM PENTOBARBITAL ALONE | NO ANALGESIA  | MORPHINE SULFATE ALONE | SODIUM PENTOBARBITAL ALONE |
| PATIENTS, NUMBER                      |                        | 54            | 97                     | 20                         | 612           | 75                     | 98                         |
| Spontaneous breathing                 | 1-30 sec.              | 90.7          | 82.5                   | 93.1                       | 97.3          | 83.0                   | 89.7                       |
|                                       | 21-60 sec.             | 3.7           | 7.2                    | 3.4                        | 1.6           | 12.0                   | 8.2                        |
| Fetal distress immediately post natal | Respiratory            | 5.6           | 24.7                   | 10.3                       | 3.4           | 24.0                   | 15.3                       |
|                                       | Pale                   | 1.9           | 0.0                    | 3.4                        | 0.7           | 4.0                    | 2.0                        |
|                                       | Limp                   | 1.9           | 10.3                   | 0.0                        | 0.2           | 2.7                    | 6.1                        |
|                                       | Circulatory            | 0.0           | 2.3                    | 0.0                        | 0.0           | 2.7                    | 4.1                        |
| Resuscitative measures                | Bulb                   | 12.9          | 15.5                   | 3.4                        | 7.7           | 14.7                   | 13.3                       |
|                                       | Friction               | 22.2          | 25.8                   | 6.9                        | 16.8          | 20.0                   | 17.3                       |
|                                       | O <sub>2</sub>         | 5.6           | 15.5                   | 3.4                        | 0.5           | 8.0                    | 6.1                        |
|                                       | Tub                    | 5.6           | 16.5                   | 3.4                        | 0.3           | 6.7                    | 6.1                        |
|                                       | Intratracheal catheter | 5.6           | 6.2                    | 0.0                        | 0.3           | 1.3                    | 4.1                        |
| Breast feeding                        |                        | 59.2          | 38.1                   | 65.4                       | 81.7          | 77.3                   | 81.6                       |
| Stillbirth and neonatal death         |                        | 0.0           | 2.3                    | 3.4                        | 1.0           | 1.3                    | 0.0                        |
| Labor                                 | Spontaneous            | 88.8          | 70.1                   | 89.6                       | 96.2          | 94.7                   | 89.7                       |
|                                       | Low forceps            | 7.4           | 25.8                   | 6.9                        | 0.5           | 4.0                    | 6.1                        |
|                                       | Other operations       | 3.7           | 4.1                    | 3.4                        | 3.3           | 1.3                    | 4.1                        |

TABLE VII. RELATION OF TIME OF ADMINISTRATION OF MORPHINE TO CONDITION AT BIRTH, NECESSITY FOR RESUSCITATION AND FATE OF BABY (STANDARD EXCLUSIONS). FIGURES REPRESENT PERCENTAGES. (NO ANALGESIC EXCEPT MORPHINE ADMINISTERED.)

|                             |                            |               | FIRST HOUR | SECOND HOUR | THIRD HOUR | MORE THAN THREE HOURS |
|-----------------------------|----------------------------|---------------|------------|-------------|------------|-----------------------|
| PATIENTS, NUMBER            |                            |               | 31         | 37          | 36         | 65                    |
| Condition at birth          | Breathed within            | 1st 30 sec.   | 90.4       | 83.8        | 72.8       | 82.1                  |
|                             |                            | 2nd 30 sec.   | 6.5        | 13.5        | 8.3        | 9.2                   |
|                             | Respiratory difficulties   | Pale and limp | 16.1       | 13.5        | 30.6       | 15.4                  |
|                             |                            |               | 3.2        | 13.5        | 8.3        | 10.8                  |
| Necessity for resuscitation | Mild measures              |               | 25.8       | 35.2        | 41.6       | 38.5                  |
|                             | Other incl. O <sub>2</sub> |               | 6.5        | 21.6        | 38.9       | 38.5                  |
| Fate of child               | Breast fed                 |               | 74.2       | 70.3        | 61.2       | 69.3                  |
|                             | Dead                       |               | 0.0        | 0.0         | 5.6        | 1.5                   |
|                             | Spontaneous labor          |               | 83.8       | 83.8        | 80.6       | 76.9                  |
|                             | Low forceps                |               | 12.9       | 16.2        | 11.1       | 20.0                  |

In three cases time interval is not stated.

Most patients received  $\frac{1}{4}$  gr., some  $\frac{1}{6}$  gr., 19 received more than  $\frac{1}{4}$  gr.

primiparas a method which is, with little doubt, the most satisfactory combination of analgesia and amnesia.

In compiling statistics on the effect of morphine on the child one should be very careful not to include in the morphine group cases in which the effect of labor itself may have caused fetal distress. Dr. Mengert has carefully excluded most of the cases in which there were other obvious causes of fetal distress. However, more consideration could be given to the numerous accidents of labor. I mention one typical example: a case in which during a protracted labor morphine was given to produce a period of rest. During several hours of sleep labor progressed normally and after six hours the head was on the perineum. At this time there was an unusual amount of bloody discharge and the fetal heart rate increased to 180. The baby was immediately delivered and examination of the placenta showed that there had been a partial separation. The baby lived but was limp and required resuscitation. The fact that morphine had been given during the labor obviously had nothing to do with the fetal distress. Cases similar to this one, and there are many, should be excluded from the list of those in which morphine had been administered when compiling statistics of this kind.

DR. EDWARD A. SCHUMANN, PHILADELPHIA, PA.—Dr. Mengert has used meticulous care in attempting to evaluate the effect of morphine but no one can do this with absolute certainty. For example, in a clinic where there is no fixed routine the primiparas who are more likely to receive morphine are the cases of inertia uteri where it is desired to give the patient a rest for eight or ten hours and it is in just these cases that there occurs the highest proportion of respiratory distress in the fetus.

In some of Dr. Mengert's cases the doses seemed rather high. In our clinic where morphine has been used by preference for some thirty years, the dosage is limited to  $\frac{1}{6}$  grain in twenty-four hours unless suppression of convulsions be required.

I feel that if a patient is given analgesia by some other drug within three or four hours of delivery to a degree comparable with that produced by morphine the effect upon the fetus will be almost identical. It is even common practice in some clinics to give morphine a short time before delivery. With regard to the elective sections done in our clinic  $\frac{1}{6}$  grain of morphine is given as a preliminary sedative before the section is begun.

DR. GEORGE W. KOSMAK, NEW YORK, N. Y.—I never hear a discussion on the subject of analgesics in labor cases that I am not reminded of an incident at Professor Sellheim's clinic in Leipzig some years ago. I was discussing with him the analgesic procedure employed in his clinic. He said, "I have a very simple little mixture here," and showed me a 250 c.c. bottle filled with a light brown liquid. He said, "It is particularly applicable to these younger primiparas. One-half dozen bottles are put into their room and they are told to take one-half the contents of a bottle when their pains become strong, and after a certain period to take another half bottle and repeat it until the labor is completed. It has no bad effects on the mother or the fetus." I asked what it was and he said, "It is just ordinary cognac, and these girls are so inebriated they do not mind labor pains."

DR. MENGERT (closing).—I am glad that Dr. Bill emphasized the rule that morphine should not be given within three hours of labor. Of course, one cannot always calculate the length of labor so accurately, but whenever possible such administration should be avoided.

DR. CURTIS.—Would you mind expressing your views in regard to giving morphine preliminary to cesarean section?

DR. MENGERT.—Generally we have not used it, although on a few occasions we have employed doses of  $\frac{1}{6}$  gr. In the few cases where morphine was used prior to cesarean section, we have seen no harmful effect from it.

hours and fifty minutes before delivery. In another instance (mentioned in the opening paragraph of this communication), an 18-year-old primigravida suffering from severe pre-eclampsia received 2 gr. of morphine in  $\frac{1}{4}$  gr. doses during the twenty hours preceding her delivery by low forceps under pudendal block anesthesia. She was in active labor for fourteen hours of this time and received  $\frac{3}{4}$  gr. of morphine during the last six hours of labor. The child, weighing 2,930 Gm. at birth, breathed spontaneously, was entirely breast fed and gained weight prior to discharge. On the other hand infants occasionally exhibited respiratory embarrassment and required resuscitative measures following doses as small as  $\frac{1}{6}$  gr. In light of the data presented, this question cannot be adequately answered.

#### CONCLUSIONS

1. The employment of morphine sulfate as an obstetric analgesic is not without some risk of postnatal, fetal, respiratory difficulty, which, however, is readily combated by the usual resuscitative measures.
2. The administration of morphine during the second- and third-hour period preceding delivery probably should be avoided.
3. Morphine seems to offer an excessive risk in premature infants.
4. On the basis of these observations, there is no good reason for the complete discontinuance of morphine as an analgesic in normal labor although its limitations should be recognized.

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#### DISCUSSION

DR. ARTHUR H. BILL, CLEVELAND, OHIO.—I have on various occasions heard members of the profession make the remark that if there were but one drug in the pharmacopeia or if they had access to only one, they would choose morphine. Dr. Mengert has pointed out some limitations and dangers associated with the use of morphine in obstetrics and has emphasized the fact that, although its administration during pregnancy and the early part of labor is without harm to the child, there is a real danger of causing apnea when it is given during the two or three hours preceding the birth. This, in my opinion, is his most important conclusion and conforms perfectly with the practice which I have followed in its use. For the most part I have used morphine in combination with other drugs, notably scopolamine. At the Cleveland Maternity Hospital, this combination has been given in a very large number of cases, more than 25,000, including both private and ward patients, with most satisfactory results and, we believe, absence of danger to the child.

There has been a strict rule that neither morphine nor scopolamine be given within three hours of the birth, and this rule has been faithfully observed in this entire series, practically the only exceptions being the occasional emergency case in which more immediate delivery seems to be imperative. We attribute the safety of this method in a very large degree to the adoption of this rule. This practice, of course, practically eliminates its use in cases of multiparas, but retains for

and thirties, because the inroads of typhoid, tuberculosis, diabetes, rheumatism, and other serious illnesses have been reduced and checked. Women have had less difficulty in childbearing; many of the complications and accidents of pregnancy have been shown to be preventable and have been eliminated to a noteworthy degree by improvements in obstetric practice.

Life tables developed by insurance companies afford further definite evidence of these changed conditions. These show that the proportion of white women born in the U. S. who reach the age of 50 was 61 per cent in 1901 and approximately 84 per cent in 1938. In other words, the average length of life in women has increased from 51 years in

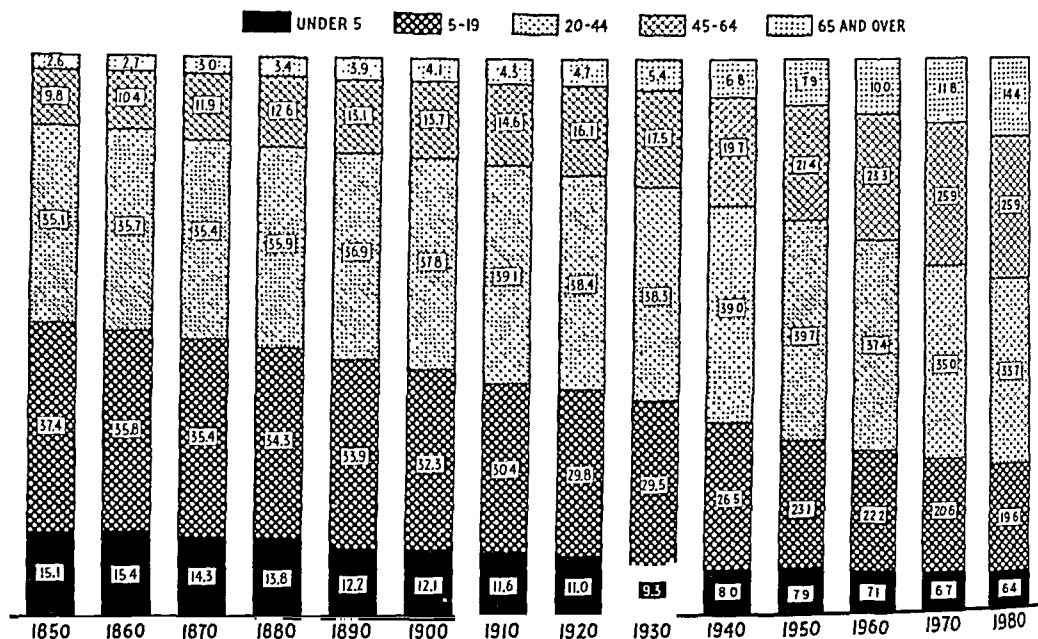


Fig. 1.—This chart shows the age distribution, observed and estimated, of the population of the United States from 1850 to 1980,\* in ten-year periods. If 65 years is accepted as the threshold of old age, it will be noted that in 1850, this group constituted 2.6 per cent of the total population. At the beginning of the century this increased to 4.1 per cent, and in 1940, to 6.8 per cent. If the present trend continues, the 65-year and over age group will comprise over 14 per cent. In actual figures, it has been estimated that the total number of these people will be 22,000,000 in 1980 as compared with 8,956,000 in 1940. (From L. I. Dublin, Metropolitan Life Insurance Company.)

1901, to 66 years in 1938, a matter of 15 years. If we examine furthermore the mortality rates with reference to age and sex we find that, among white persons in a large industrial insurance group (the Metropolitan Life), the excess of male over female mortality is at a minimum in the age group of from 20 to 24 years. Obviously this is due to the special risk of maternity incurred by women during this period. When we go a step farther along in life, the highest excess mortality among males over females is in the age group of from 45 to 54, where it is over 50 per cent. At this time the dangers of childbirth are over among women but, on the other hand, the occupational risks have increased among males. A comparison of these carefully studied figures with those of the general population will disclose little difference.

\*1850 to 1940, from United States census data. 1950 to 1980 estimated by Thompson and Whelpton.

## Special Article

### GYNECOLOGIC AND OTHER IMPLICATIONS WHICH RELATE TO AN AGEING FEMALE POPULATION\*

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IT WOULD appear from available statistical information and common observation that, as a nation, we are growing older. If this is a proved fact, and it seems to be so, does it not mean that we are faced with new problems in the care of a group of older people? I may not be able to make an adequate answer within the limits of this presentation because the question to be discussed has wide implications. But there seems to be enough factual information at hand to demand our attention, and it may be opportune to review the situation and to develop the necessary interest among all physicians, including the gynecologist, for its further consideration.

Statisticians are telling us that life expectancy has been extended in comparatively recent decades, that the average span of life among the people of this country has been lengthened from approximately 35 years in 1850 to over 60 years in 1930. In subsequent years it should be even longer. Perhaps by 1960 it may be from 70 to 75 years. In other words, there are more young children and more old people today than there were less than a century ago. These facts have more than a statistical interest, they have definite sociologic, eugenic, and medical implications which, in many ways, are closely related.

Pertinent to our subject, it is necessary to define two words which have come into our medical vocabulary, *gerontology*, which deals with the problems of ageing, and *geriatrics*, which is concerned with the related diseases. Efforts at alleviation of the diseases and other disturbances associated with declining years do not imply a renewed search for the proverbial Fountain of Youth, but a search for the means by which this period of life may be made one of happiness, satisfaction, and comfort rather than of depression, invalidism, and dependency, or of a mere prolongation of what may appear as a useless and unproductive existence.

The particular scope of this paper is centered on women who, while participating with men in similar ailments of advancing years, present certain problems of their own.

Female life expectancy, according to the last U. S. Census, covering the decade from 1930 to 1939, is now 64.5 years as compared with 60.6 for men. In 1900 it was 51 against 48. Life expectancy is, of course, a mathematical average of all persons born alive, and the increase has been developed in great part through the lower death rate in the young. Today the infant mortality rate is 57 per 1,000 for male babies and 53 for females, as compared with 133 and 111, respectively, in 1900. Likewise more young people are living through their twenties

\*Presented, at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.

groups of investigators who have delved into the problem. A perusal of these references unfortunately discloses that, with few exceptions, the clinician, as such, has taken little part. The biologist, the anatomist, the physiologist, the statistician, the pathologist, the anthropologist, and the sociologist have all made noteworthy contributions in a problem to which the clinician, in a broad sense, does not appear to have accorded enough attention.

It would appear appropriate at this point, to attempt a definition of what we mean by old age. Generally speaking, it is a relative term. A human being is born, matures, and then remains stationary or declines. But can we state positively that the latter period should be designated as "old age"? Certain aspects of maturity are closely combined with the latter period, yet this may have little effect on individual activity or personal worth. Some people are more worthwhile and more competent and better able to take care of themselves at sixty than others are at forty. Therefore it would be preferable to measure old age not by years but by competency, both physical and mental, and not to sidetrack people over fifty into the limbo of forgetfulness in so far as their productive and other capacities are concerned.

Admitting an increase in the span of life, how may we account for our increasing number of old people? We must acknowledge among other factors that the saturation point in opening up new frontiers had ceased, practically speaking, at the opening of the century and that the perils of frontier life had diminished, especially for women. Moreover, emigration from less favorable regions abroad has diminished in the last forty years, with a lesser incidence of previously acquired illnesses due to inadequate diet, severe muscular labor, exposure, etc. We see this reflected particularly in the reduced incidence of rickets and bone tuberculosis, among other crippling conditions, with their possible effect on childbirth. The advances in preventive medicine likewise have become more widely applied in most American communities and therefore inroads of devastating illness have been checked.

While women have participated with men in the generally improved conditions of modern civilization, they present as a class another interesting picture. Among other things, it must be acknowledged that within our generation a great psychologic change has taken place. Women not only have become emancipated in a political and social sense, but they have endeavored to sidetrack old age in so far as personal appearance and activity are concerned. No longer is the woman of fifty, even if she be a grandmother, satisfied to put on what were formerly regarded as the habiliments of that period. She endeavors to preserve her figure, she clothes herself in raiment of a pattern like that of her daughter, she participates in the activities of youth to an extent which often is a discomfort and embarrassment to the opposite sex. She refuses, in other words, to become old. Sooner or later, naturally, she must succumb, but she does it with more resistance and all this may, and probably has helped, to prolong her life, aside from what we doctors have claimed to have done in our efforts to improve her health. That woman is as old as she looks, was never a truer proverb than it is today.

However, the recital of all these pleasant things cannot deter us from giving careful thought to the inevitable consequence of failing vital functions and other matters, which even the beauty specialist cannot hide or overcome.

It is further evident from the U. S. Census figures, that all ages have shared in the improvement of mortality rates since the beginning of the century and, if favorable environment, social changes, and medical care can be distributed as universally as possible in what still may be called an imperfect world, the expectation of a longer life may be increased even further. For it has been demonstrated that the various hazards to life, including diseases, accidents, etc., have all been reduced during this period to much lower figures.

Women as a class, however, need to be studied from a somewhat different point of view. It has been assumed that their greatest risk is concerned with their reproductive functions which naturally present a hazard to which men are not subject. A distinction naturally must be drawn here between disease and function. In the male there is little or no disturbance which can be compared with the more serious risk of pregnancy, with its always uncertain dangers of toxemia, hemorrhage, infection, and the trauma incident to labor. Aside from unavoidable accidents, many of these complications of pregnancy can be avoided by adequate obstetric care. Evidently the latter has accomplished good results, because today there is less crippling of prospective mothers, consequently a greater number of them go through the period of hazard and are therefore more likely to have their lives prolonged. As for the menopause, this need not necessarily produce the generally expected disturbances, in view of the increasing knowledge of the effect of hormonal medication and of better general health among adult women.

It may safely be claimed therefore that the lowered mortality from the hazards of childbearing, from the reduction of various disease entities, from improved living and social conditions, has increased the life span of women. On the other hand we must consider as contrasting factors, those associated with degenerative and other illnesses of advancing years and the social, economic, and other pertinent conditions which come into relation with this period. The diseases include mainly those of the circulatory, digestive, nervous, and reproductive organs, as well as the disorders of nutrition and metabolism. An estimate of their incidence is difficult, but here again, a valuable clue may be obtained from the records of insurance companies, particularly those of the industrial type. The mortality rates among female insured persons in the Metropolitan Life, as an example, have moved downward rapidly in the earlier years for tuberculosis, diabetes, heart disease, and other illnesses, due undoubtedly to improved health measures and better medical care. However in the group of women beyond the period in which these more or less acute illnesses preponderate, there will be noted an increase in the number of deaths due to degenerative diseases of the heart, blood vessels, kidneys, and other organs, and of new growths. In other words, as women grow older, they develop many of the ailments once believed characteristic of the opposite sex, once they have survived the hazards of their childbearing years. It is unfortunate, however, that the doctor does not always have this fact in mind and that too often he attributes what are degenerative or alterative processes, in middle-aged women in particular, to mere menopausal or allied disturbances. And so the gynecologist must extend his field of observation beyond the limited sphere of the pelvic organs and become likewise an internist.

In recent years a great interest in the aged has been developed. One is amazed by the extensive literature and by the number and the varied



## NUTRITION AND METABOLISM

For centuries the importance of proper and adequate nutrition in preserving life has been acknowledged yet, until recently, more attention has been accorded to infancy and youth than to mature life. The fact must not be lost sight of that rapid chemical change is prevalent in youth, for the need of adequate growth is more essential during that period. After this is attained, the requirements are lessened, although the desires and opportunities for change in foods perhaps are more easily gratified and overindulgence or false indulgence may prevail. Moreover, because of the diminishing rate of chemical change, it requires more time to produce a desired effect. The relative admixtures of proteins, fats, and carbohydrates needed in older people have not been fully determined nor can we hope for careful calorie measurements as a guide in ordinary life. An average of 2,500 calories for a hard-working woman is apparently excessive for one leading a sedentary existence. Women, as a rule, indulge freely in carbohydrates, a tendency which it seems can be curbed only with difficulty.

Unfortunately there is insufficient clinical evidence to demonstrate the effect of specific diets in man—observations in lower animals have been relied upon largely for information. However, in recent years laboratory research has been conducted by a number of investigators who claim that diets rich in vitamins and poor in purified foodstuffs have an influence in preventing degenerative diseases. But the question of essential protein intake is still in dispute, and whether this, e.g., shall be from milk or meat, is open to question, as well as the effect on kidneys and blood vessels, measured by the consequent occurrence of chronic nephritis or hypertension.

Basal metabolism shows a definite decline with the onset of years. As the body fails, the rate frequently diminishes with other functions, but variations in values indicate that senescence is more than a matter of time. While the ability to digest would seem impaired with increasing age, the ability to utilize food does not appear to be greatly affected, for there is little evidence, among other things, of any progressive senile atrophy of the gastric and intestinal mucosa.

Changes in the mineral content of the body, in the tissue fluids, in fats and other substances, have all been studied and shown to vary from youth to old age, but about the underlying biochemical processes we have scant information. A cooperative attack is needed to confirm the hope that life can be prolonged by manipulating the diet. At any rate, if limitations can be formulated, this may avoid the distress associated with digestion in so many old people.

## ORGANIC DISEASES

Changes in the essential organs necessary for the maintenance of life, are usually associated with declining years. These include the nervous, circulatory, digestive, genitourinary, osseous, muscular, and glandular systems. The male sex may present a preponderance in one group, the female in another, but with few exceptions, we find an incidence more or less equal in both. Let us review some of these briefly.

*Nervous System.*—Aside from the acute mental disturbances of which the origin may be in question, a relationship between nervous involution and arteriosclerosis has generally been assumed and mental senility, cerebral accidents and other phenomena attributed to the same. All

The life span of women may be considered in three periods. The first ends with maturity, as interpreted by the ability to conceive, the second includes the years of reproductive capacity, the third comprises a period of rest and retrogression. In all of these the collected organs of generation play an outstanding part, but they are closely integrated in their functions and development with the other systems in the body which serve to maintain life and in its various phases.

The question as to the reasons why more women reach an advanced age has already been referred to. How does this affect the larger aspects of the medical and social problems in which physicians have an interest? For a possible solution we must approach the subject from various angles. Leaving aside other factors, it may be said that a better knowledge of the growing organism and maintaining it in good health, have brought more young women through the critical period of child-bearing with less damage. This applies in particular to the better knowledge of endocrinologic disturbances and their treatment in young and middle-aged women, as well as to the advances in obstetric care. While much remains to be done in the latter field, the reduced puerperal mortality rate and the greater salvage of infant life are evidences of accomplishment. It means that fewer women are crippled by child-bearing and that they reach their later years in a better condition of health. In addition, we may expect a lesser incidence of those degenerative diseases, particularly of the heart and kidneys, which may be traced to a lowering of the occurrence of the formerly more common infectious diseases.

Granting the above factors, among others, as productive of an increased older age group among women, the admission must be made that in consequence we are faced with a larger incidence of those diseases of a purely degenerative type peculiar to advanced age. And in this connection, one cannot discuss the medical implications of an increasing number of ageing people without considering the social problems involved. If inability to care for themselves develops, is it incumbent upon society to undertake the task? If there are more dependents in the years to follow, is the burden for their care to be saddled on the younger generation? Can we accomplish the desired end by increasing the number of almshouses and similar institutions, by various old-age security measures or by politically engendered pension schemes? As physicians we may have less interest in these phases of the subject, but we have a responsibility as regards the medical implications of the problem. Preventive measures must be developed to avoid what have been regarded as the unavoidable accompaniments of old age and curative measures employed when we develop, after due study, the necessary technical knowledge. An ounce of prevention is nowhere more effective than a pound of cure than in this particular field of medical practice.

It is not feasible within the limits of this presentation to discuss fully the symptoms and treatment of the various illnesses that pertain to the ageing group of women. We can refer only briefly to some which appear more noteworthy in a general sense and follow this with the gynecologic implications of the problem. This includes the nutritional and metabolic disorders, the organic diseases, and the mental and psychologic aspects, as among the more noteworthy.

plasm. The psychologic effect of satisfactory bowel evacuations varies with the individual. Elderly women grow careless, with resulting obstipation, and this calls for adequate treatment. Perhaps the dictum of the great American humorist, Josh Billings, still holds, namely, that "a good reliable set of bowels is worth more than any quantity of brains."

*Urinary System.*—It is generally assumed that the kidneys fail in old age. Death from this cause results perhaps more frequently in men than in women. However, if primary senescent involution does occur, its effects, according to several authorities, are overshadowed by the secondary tissue changes which follow normal ageing of the renal arteries. The lack of a proper blood supply and the resultant hypertension seem to be the factors which cause the disturbances. The practical value of these conclusions may in time be reflected largely in timely preventive measures yet not fully understood or capable of practical application.

*Reproductive System.*—Advancing age in woman is associated with the decline in her reproductive powers, and the menopause has been regarded as the dividing line. Yet we must admit that in a general sense this is not true. The reproductive period may have ceased, genital atrophy may begin, the sexual function may wane, but how many women today feel that they should be labeled as "old" at this time? The menopause occurs while other bodily functions frequently are still in their prime. Its accompanying disturbances may be effectively treated in ordinary cases, as well as in those where it has been induced artificially. However, hormone therapy has met with such good results that it is administered very frequently in a haphazard fashion. The pituitary and the thyroid have an importance perhaps equalling that of the ovary, yet these glands are generally disregarded in the prescriptions for treatment. The estrogenic substances, as such, should be given as a measure of alleviation for the disturbances associated with diminishing ovarian function, not to prolong the latter.

The possible occurrence of cancer of the generative organs constitutes the greatest source of concern to women. There is a tendency toward various neoplastic diseases at, or after, the menopause, in which the breasts, the ovaries, the uterus, and accessory structures may participate, but these are not necessarily all malignant. Just what effect hormonal changes may exert on the production of malignant tumors in women, has not been determined definitely. More recently it has been claimed that it is due to an endocrine imbalance involving the pituitary and adrenals. Vitamin disturbances are also accused. Cancer is an uncontrolled growth and just what removes the restraint in certain organs, when others continue to function normally in the ageing body, is unknown. Perhaps at some future time we can regulate the process but at present, early recognition and appropriate surgical or radiation treatment probably offer the best solution.

The incidence and mortality from cancer of the female generative organs constitute a field of wide interest and cannot be summarized briefly. Collected statistics have been developed by various agencies of which those made in New York probably reflect the situation throughout this country. In New York City, T. J. Duffield, Registrar of Vital Statistics of the Department of Health, states that cancer ranks second among the leading causes of death and the recorded cases in New York City have increased about 73 per cent since 1901. Unquestionably some

this is covered by the formerly popular designation of "hardening of the arteries." Yet with the more routine and widespread employment of actual blood pressure measurements, we often find abnormally high readings in younger people and equally low readings in the aged. Older men do not appear to have a monopoly of high blood pressures; women also are afflicted and are more puzzling subjects for treatment, because generally there cannot be the ready resort to such precautionary advice as restrictions in alcohol, tobacco, and perhaps certain foods, the abuse of which usually is associated with the male sex. Some neurologists have asserted that ageing of the nervous system is independent of degenerative changes of the cerebrospinal blood vessels and, although these may be associated, there is no direct causal relationship between arteriosclerosis and cerebral involution. On the other hand, the more acute apoplexies and thromboses can be attributed only to arterial sclerosis, so that attention must continue to be extended to preventive measures in earlier life if we want to avoid their destructive effects later on.

*Circulatory System.*—In considering the circulatory system in ageing persons, we must take into account both the structural and functional changes. The demands on the heart vary greatly from youth to old age. In earlier life it is more liable to reflect the effects of infectious disease and, in women, such damage is often aggravated by the processes of childbearing. But, as a rule, the strain on the heart is less in women than in men. Yet the organ undergoes alterations in the course of time, and it would be desirable to have established a normal curve for cardiac activity and function which can be employed for successive decades of life. Surely a desirably functioning heart in a woman of 70 would present different standards from that of a woman of 30. We should have practical methods for ready estimations and perhaps the electrocardiograph experts in time will furnish them. In this connection we must also take note of the altered composition of the blood, considering this as an organ, and of the antibodies and other essential constituents which vary with age.

*Digestive System.*—It is generally accepted that digestion wanes with age. How much of prevailing indigestion may be due to previous indiscretions and how much to an actual wearing-out process, is not yet clarified. It has been shown that the quantity of saliva diminishes and likewise the ability to secrete hydrochloric acid freely after eating. However, there is little evidence to show that the gastric mucosa itself undergoes much change. Achlorhydria may be compatible with good health but predisposes to anemia, inadequate calcification of bone, and enteritis. Although the death rate from ulcers of the stomach or duodenum increases with age, their onset rarely occurs after 60. The relation between gastric ulcer and cancer is still debatable but it is stated that after 45, gastric cancer causes death 6 to 7 times more frequently than ulcer. As for liver changes, the cirrhotic processes associated with advanced years are believed to be due to pathologic conditions rather than to senescence. The stasis of the gall bladder associated with pregnancy is claimed to be responsible for the higher mortality in women from diseases of this organ in later life. Hernias, adhesions, and neoplasms, with consequent obstruction, increase with age but are amenable to treatment in a surprising number of cases. While constipation is usually assumed to be an accompaniment of old age, it has been shown that it is usually a lifelong complaint and, if of recent onset, indicates most frequently an obstructive neo-

values. Youth associates its own period with activity and progress and regards advancing age as characterized by lack of desire, satisfaction with past accomplishment and general resignation. Wisdom as a result of accumulated experience is not always accorded to age by youth. This is well shown by the impatience shown by young women toward the ideas of marriage and childbearing entertained by their mothers and grandmothers. However, it should be acknowledged, although perhaps grudgingly by youth, that mental capacity, among other things, is not necessarily measured by years of existence and that actual mental derangement is not necessarily an accompaniment of old age. Naturally, we must admit that, among organic systems, including the nervous, deterioration in an anatomic and physiologic sense must result in dysfunction for the process is irreversible, but we are by no means certain of the effect of environmental and other factors and of personality changes. It may be possible that further exploration by the psychotherapist will lead to the correction of influences that are depressive in character and that the personality changes so characteristic in older people may become less prominent as reasons for relegating them into the discard. Moreover, I cannot agree with the claim of so many psychologists that sexual impotency alone is the basis for mental retrogression in the aged or that it would not be possible to develop a feeling of contentment by a properly preserved state of good general health outside of the sexual sphere. Women perhaps manifest less evident disturbances in the latter than men, because they are untroubled by such distressing factors as an enlarged prostate and its complications.

Leaving out of consideration such definite disturbances as actual senile dementia and bearing in mind that ordinary changes in personality are not to be magnified into evidences of unconquerable senility, it becomes essential in this complex society of ours to develop new social adjustments between young and old, so that the best functions of all ages can be fitted into a scheme in which individual differences, rather than age differences, are more fully stressed, as so well stated by Walter R. Miles in Crowder's book on the *Problems of Ageing*.

Perhaps I will be regarded as wandering from my thesis in stating that, in my belief, there are certain eugenic factors that enter into the consideration of the problem of the ageing woman. The eugenists have called attention to the importance of selective breeding, not only among domestic animals but among human beings. Healthy children demand healthy parents for their creation, and children who have a good physical start in life are more likely to reach and go through advanced years with less difficulty and, in consequence, with greater independence. In other words, competent and responsible married couples should have more children than their irresponsible neighbors. Unfortunately that is not the sort of society which prevails today and pregnancy seems governed largely by the elements of chance and expediency. A solution would be offered if it were made possible for young people to begin parenthood earlier without jeopardizing their standard of living, and if as much attention were given to methods for favoring conception as for those devoted to its prevention. Only too frequently the favorable time for pregnancy is postponed for social and other reasons. The best period for childbearing is believed to be in the twenties and early thirties. Although women now live longer, their procreative period remains the same, and we cannot hope for babies when ovulation ceases.

of the increase in the latter has been due to improvements in diagnostic methods and to a wider opportunity for their use, but we can also attribute it to the increases in the middle and older age groups, where cancer is likely to be more frequent. In 1901 only 3.5 per cent of the deaths in New York City were charged to cancer; in 1940 this had increased to 16.2 per cent. This includes both sexes but it is of interest that death rates among males slightly exceed those among females, contrary to the popular belief.

L. C. Kress, Director of the Division of Cancer Control of the State Department of Health, favored me with a recent report of the situation in New York, excluding the greater City, during 1941. The case rate of reported cancer of the female genital organs in New York State per 100,000 population, was 7.13 during the age group from 55 to 64; 17.44, in that from 65 to 74; and 25.37, at over 75 years. The corresponding death rates in the same age groups were 4.99, 11.99, and 14.99 and the case-death rate ratios were 1.43, 1.45, and 1.69.

In the detailed table submitted with this summary, the ratios between case rates and death rates show a definite decrease in each succeeding ten-year period from 35 to 75 years. Although the degenerative diseases undoubtedly play a great part in causing deaths in older people, the death certificates give preference to cancer, where this is mentioned either as primary or secondary cause, over other diseases except those of a communicable or accidental nature. What direct effect increasing age, with its weakening factors, may have on this ratio cannot be estimated from the statistics on hand, so that my belief that cancer possibly is less malignant in older women must, for the present at least, remain a matter of doubt.

Unfortunately the incidence of malignancy in the population as a whole is not known definitely, so that we are unable to estimate without further study what actual improvement in the handling of cancer cases has resulted from more modern methods of treatment. Perhaps this would constitute an interesting topic for study by a committee from this Society.

#### OTHER ORGANS AND SYSTEMS

Time does not permit a discussion of the changes which take place in the bones, muscles, joints, teeth, skin, and the organs of special sense. These are mostly accepted as evidences of advancing age. But much can be done in the way both of palliative and curative measures to reduce the attending disturbances and crippling effects. Nor have I included any detailed references to the respiratory diseases, which figure so largely in the mortality rates of the aged and in which lowered resistance is often the determining factor.

Pneumonia may well be considered with influenza and affects every period of life, although most prevalent at the two extremes and more among men than women. Pneumonia of all types is a very dangerous disease at any age, but advances made in diagnosis and treatment will undoubtedly lessen its fatality rate even among the aged, in whom it so often constitutes a terminal condition. The control of pneumonia remains a public health problem of the first magnitude.

In addition to the foregoing, psychologic manifestations associated with the advent of old age are accepted quite casually as a usual accompaniment. It depends, however, upon who makes the estimate, for youth and older people are by no means in agreement as to relative

these were major cases and there were no operative deaths. The anesthesia used was ethylene, with one exception. Dr. Danforth feels that if the patient is in good general health, is properly prepared, handled expeditiously and nontraumatically, the risk of surgery is little, if any, greater than in younger women.

I am convinced that a wider inquiry would have elicited reports of equally favorable results. Where operative interference is indicated in the group of older women, there need be less hesitancy in attacking gynecologic problems because of the better understanding of the underlying factors and the developments in pre- and postoperative care and improved anesthetic procedures.

#### SUMMARY AND CONCLUSIONS

You may well ask, What has been the purpose of this presentation? What has been demonstrated and what can we, as physicians, do about a problem which demands our attention as it does that of other interested and affiliated groups? For there are definite medical implications associated with advanced age, which we cannot disregard. If, owing to the progress developed in various fields of endeavor, men and women, broadly speaking, have grown older, what can be done to make this period one of comfort rather than infirmity and debility? As doctors we must be prepared to develop a new field of activity based on more adequate information about the processes of ageing and their amelioration where this is possible. In this connection it is essential to acquire a knowledge of the criteria of physiologic age and not assume, as in the past, that functional and anatomic depreciation parallels chronologic time. For example, in women, as I have stated, the hormonal changes in the climacteric have received special and rather one-sided attention, while the role of vascular changes, the nutritional problems, the psychologic adaptation to advancing years and other features, have been given less thought and consideration.

It may become necessary, in order to appreciate "old age," to revise our method of thinking, perhaps to revise some of our methods of education in medicine. Our students are largely taught by examples of abnormalities without sufficient knowledge of the normal. Their minds are being burdened by the attempt to absorb factual information, often dubious and ill documented, which has developed as the result of the so-called progress in medicine but which, because of its enormous proportions, cannot be digested adequately. And this admission may well be applied to our thesis, namely, the care of our ageing population, for perhaps, as physicians, we have concentrated on the abnormal and neglected the normal status. Unless the latter is definitely and completely understood, we can make no progress in our knowledge of what happens when it goes wrong. We were prone to accept a definite life span and have counted it by years. Now we are finding that perhaps this is false, that the functioning of the human organism depends not alone on mere ageing processes but on the influences of environment, of wear and tear, of proper food and its assimilation, of physical care and sensible living. In other words, prevention, the earlier recognition of destructive agencies, and a wider knowledge of their causative effects are of equal importance with the sociologic developments which have assumed the chief note in the care of old people. I would regard limitation to the latter as a defeatist measure, surely not commensurate

We cannot balance infertility in youth by looking forward to its recrudescence at an age when economic conditions may be more favorable. Therefore, we may hope for a healthier group of older women if their childbearing are limited to the proper age and number of offspring, even if we cannot proceed further from the standpoint of eugenic selection. No doubt, such philosophy will be disputed, but some day it will prevail when reason rather than chance can dictate in the matter.

#### OPERATIONS ON OLDER WOMEN

The question of operations in an increasing number of older women has necessitated a resort to changes in procedures which were designed primarily for a younger and more virile group. This applies particularly to pre- and postoperative handling as well as to the important detail of anesthesia. Sufficient evidence is at hand, however, to warrant and permit necessary operative intervention, when indicated, in elderly women who, in former years, would have been turned down as too great a risk.

Several of my colleagues in response to questionnaires have favored me very kindly with their statistics and opinions on this subject.

Dr. Richard TeLinde, reporting on the gynecologic service at Johns Hopkins Hospital, states that 167, or 4.1 per cent, out of a total of 4,071 patients entered from Jan. 1, 1940, to Jan. 1, 1942, were 60 years and over. Included here were 112 operations of practically all types, with the following results: well, 41; improved, 61; unimproved, 7; died, 3. The deaths were ascribed to coronary occlusion and pyelonephritis, and one was moribund with carcinoma of the bladder. Dr. TeLinde prefers pentothal sodium as an anesthetic in this age group.

Dr. Robert T. Mussey, of the Mayo Clinic, states that during a similar period of two years (1939 to 1941), among 27,140 patients admitted, gynecologic patients over 60 years of age numbered 2,430, including 390 breast cases. Operations were done on 585, with 3 deaths; including one each from pulmonary embolism, glomerulonephritis with uremia, and pneumonia. Four hundred thirteen patients were operated upon for rectocele, cystocele, and prolapse, with over 95 per cent either completely cured or improved. For malignant lesions of the breast, among 390 cases, a five-year survival rate of 75 per cent was noted for patients without axillary metastases and 30 per cent with metastases. The five-year survival rate for malignancies of the pelvic organs was 55 per cent. General anesthesia was usually employed, with spinal in a fair proportion of suitable cases.

Dr. Alice Maxwell, of the University of California Hospital in San Francisco, states that among 680 gynecologic admissions during 1939, 69 patients were over 60, many of these over 70. There were no operative deaths. She was impressed by the absence of postoperative complications, no pneumonias or vascular accidents, although many of the patients had a hypertension and two were diabetics.

Dr. William E. Studdiford, reporting from Bellevue, one of the largest New York City municipal hospitals, with an extensive charity service, stated that among 7,971 gynecologic patients in a recent year, 154 were over 60 years of age. Sixty-three operations were performed, of which 28 were of a major character. A total of 19 deaths occurred in the entire series of cases, of which 10 are claimed to be nonoperative.

Dr. W. C. Danforth had 63 operative cases in patients between 60 and 75 years of age, including breast cancers. With a few exceptions



come to determine if there are cervical injuries, erosions, etc., we would detect cancer much earlier and greatly benefit our patients.

In conclusion, one word as to the question of prolonging life: Where are we going? Where is this increase in age taking us? Are we adding years to a useful life, or are we merely prolonging existence? I feel that women who have reached 70 to 80 years of age should be trained in some form of occupational therapy, and should have something that will keep their minds and fingers active. If not, they will degenerate mentally, become a burden to the family, and will cease to get any joy out of life. Mere prolongation of existence is not enough. We must strive in every way to keep up the mental activity as well as the physical well-being of these women.

DR. CURTIS F. BURNAM, BALTIMORE, MD.—The question of when old age begins is a very interesting one. We know that the time of the menopause varies enormously among individuals, starting in the thirties and sometimes going far up into the fifties. Old age, for instance, as far as the ears are concerned, apparently begins at about ten years of age. I am informed that audiometer tests on a large number of children and older people show that acute hearing of high tones and range of tones is greatest at about 9 or 10 years of age, and if tests are made 10 years later nobody can hear noises that one could hear at 9, and that diminution in acuity goes straight on through to the end of life. I suppose the same thing is true of many other functions of organs in the body. However, I might say that the ears are still very useful to people in the ordinary work of life for a great many years. A great many octogenarians still have ears that are satisfactory for ordinary use.

DR. KOSMAK (closing).—I have nothing further to say except to express my appreciation of Dr. Taussig's remark that this was a philosophic paper. I would not have dared label it as such myself. I will say that my interest in this subject led to a great deal of reading and I must apologize for having been unable to do more than just sketch the outlines of this enormous field which is now beginning to interest the medical world.

As Dr. Taussig has said, it would be a most desirable thing if we could imitate "well baby clinics" for women of middle age in an effort to detect not only the possible malignancies but also the beginning of other degenerative diseases. I think the subject is one into which even a gynecological society might well expand its labors.

*(The remaining papers presented at this meeting will be included in the December issue.)*

with an advanced and modern method of thought. I would repeat that the almshouse and the home for the aged do not afford the solution. I feel that we must look for the answer elsewhere, by stimulating the thoughts of the medical profession and its allied workers along new lines, rather than merely relegating the increasing numbers of our old people to a domain of despair and uselessness.

Whether we agree or disagree on the solution, there is sufficient evidence which, in part at least, I have endeavored to outline, that the proportion of older people in civilized countries is increasing decade by decade. It would appear essential therefore not only to admit the facts but to enlist and develop our resources for the welfare of the group whether by individual or collective measures. Tissue life may have limitations but these limitations will not be cut short by degeneration and disease to the same degree in the future as they have in the past, for it is unreasonable to believe that the preventive measures which are now operating will become lessened in the will to prolong life and to postpone the advent of death.

NOTE.—In the preparation of this paper I desire to acknowledge my indebtedness to the data and writings of Drs. L. I. Dublin and A. Lotka, of the Metropolitan Life Insurance Company, to Dr. E. V. Crowdry and the contributors to his outstanding compilation entitled *Problems of Ageing*, and to various other authors whose articles have been consulted, including William Cramer, M. W. Thewlis, Müller-Deham, and C. C. Little.

23 EAST 93RD STREET

#### DISCUSSION

DR. FREDERICK J. TAUSSIG, ST. LOUIS, MO.—It is very difficult to discuss a broadly philosophic paper such as Dr. Kosmak's and I can only touch upon two or three points. May I first of all concur with what he had to say regarding the tendency to ascribe too many and too various symptoms to the change of life or menopause. The routine administration of stilbestrol, as done by many practitioners and some of our own specialists, is wrong, because in each case we should try to analyze the patient's psychic and physical condition to see how much influence that has on her general well-being before prescribing endocrine therapy.

There is no doubt that this change in age incidence is going to increase the number of patients who reach the cancer age and that malignancy will become an increasingly important topic for us to consider in our therapy.

If we compare the programs of today with those of the beginning years of our Society we will note a marked difference in the character of papers presented. Then there were many more papers on inflammatory conditions of the adnexa and pelvic injuries than at the present time. I feel therefore that a study of the patients who have reached the cancer age is of great significance. We should, and many of us doubtless do, have patients come to us for a check-up regularly between the ages of 40 and 60. I have at the present time a very large number of women who come to me twice a year, sometimes oftener, for such a physical check-up. And when this is done I do not confine myself to the pelvic examinations but invariably examine the breasts, take blood pressure and urinalysis and, if necessary, refer them to an internist. Now that is all right so far as the private patient is concerned. I wonder whether we are doing our duty to our clinic patients. We have established baby clinics for a check-up on well babies. It seems to me that a similar check-up clinic should be established for examinations of women in the menopause age. If we could establish as part of our *dispensary* service such a clinic to which women between the ages of 40 and 60, without any symptoms, could

Beginning with 0.1 mg. once or twice a day, the dosage is gradually increased if necessary. With discriminate selection of cases and judicious use of dosage schedule, uniformly gratifying results were secured. The use of bile salts or acids tended to prevent or allay untoward gastrointestinal complaints.

Use of pellets of crystalline stilbestrol injected under the skin of the thigh appears to offer great promise of being an ideal form of therapy in the menopausal patient, provided the proper indications for this type of therapy are carefully observed. In ointment form in a concentration of 10 to 20 mg. per ounce, applied locally in patients with simple senile vaginitis associated with pruritus vulvae, it yields uniformly good results.

In the dose of 0.1 mg. per os or in the form of vaginal suppositories it proved efficacious in the treatment of gonorrheal vulvovaginitis in children.

J. P. GREENHILL

Cope, C. L.: Excretion of Pregnandiol and Corpus Luteum, Clin. Sc. 4: 217, 1940.

Cope presents clinical material which confirms the principal claims of Venning and Browne that pregnanediol is excreted in the urine only during corpus luteum activity. Excision of the corpus luteum during early pregnancy results in a rapid fall to zero of the pregnanediol excretion, which normally continues in increasing amounts to full term. Pregnanediol is excreted during the luteal phase of the menstrual cycle, falls to zero before bleeding commences and is absent from the urine during the first, or pre-ovulatory, half of the cycle. In contrast to this, no such excretion of pregnanediol occurred over a period of several weeks in two women with secondary amenorrhea in whom it was unlikely that ovulation was occurring. No pregnanediol was excreted during three excessive uterine bleedings of a woman with a diagnosis of nonovulatory bleeding. This provides additional evidence of the close association between corpus luteum activity and pregnanediol excretion and is compatible with the main thesis of Venning and Browne. However, activity of a corpus luteum in nonpregnant women is usually associated with a secretory type of endometrium.

The fact that the corpus luteum of pregnancy may be removed at the second or even the first month without abortion has led to the assumption that under these conditions the chorionic villi take over the hormone-producing function of the corpus luteum. Since this seems probable, Cope feels that adoption of a similar endocrine function by the normal premenstrual secretory endometrium is not an impossibility. Injection of progesterone in women not excreting any pregnanediol caused a small but definite amount of the substance to appear in the urine. In view of this, it is not justifiable to assume that the magnitude of pregnanediol excretion necessarily gives any quantitative indication of the rate of progesterone production by the corpus luteum. The state of the endometrium might prove an important factor in determining the percentage yield of pregnanediol from a given quantity of progesterone. However, pregnanediol excretion curves may reflect the state of the endometrium more closely than the activity of the corpus luteum. Until contrary evidence is available, one must assume that the observed pregnanediol excretion represents only a small proportion of the total endogenous progesterone production. Therefore it must be determined whether pregnanediol is the most important excretory product of endogenous progesterone. Available evidence does not reveal appreciable quantities of any substance in the urine other than pregnanediol glucuronide and allopregnanediol, probably also present as a glucuronide, which might be considered a breakdown product of progesterone metabolism.

Cope concludes that pregnanediol excretion is a qualitative indication of corpus luteum activity in the nonpregnant woman and that it probably indicates progesterone

# Department of Reviews and Abstracts

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## Selected Abstracts

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### Endocrinology

**Smith, George Van S.:** *The Use of Female Sex Hormones in Disorders of Women*, New England J. Med. 225: 719, 1941.

A brief discussion of the efficacy of various female sex hormones in the treatment of amenorrhea, dysmenorrhea, premenstrual distress, uterine bleeding, habitual abortion, sterility, senile vaginitis, vulval itching and cystic disease of the mammary glands concludes with the following statement:

"The practical use of female sex hormones in disorders of women is indeed still limited. Clinical trials are vastly easier than fundamental investigation, but until more basic knowledge is acquired, voluminous contradictory and poorly controlled results will continue to appear and bewilder even those who are supposed to have more than average familiarity with the field. Many physicians believe that they are behind the times in the matter of hormone treatment and that others can accomplish more than they can. From my own experience, in practice and laboratory and from a fairly intimate acquaintance with the literature, I can assure them that they really are not behind the times, for just as soon as treatment is found to be clearly and consistently effective, it rapidly comes into universal use. Only estrogen, alone, in the treatment of the menopause has reached that goal."

HUGO EHRENFEST

**Abarbanel, A. R., and Klein, Milton D.:** *Clinical Experiences With Stilbestrol*, New York State J. Med. 41: 383, 1941.

It was found that the synthetic estrogen stilbestrol in dosages up to 500 mg. does not affect established lactation in the nursing human being. If given in doses up to 1,000 mg. (1 Gm.) in divided doses beginning soon after parturition, it will not prevent onset of lactation in the nursing human being, although the appearance of the average normal amount of milk secretion will be delayed until two or six days after the last dose of stilbestrol, provided the baby continues to nurse.

In doses of 25 to 40 mg., it prevented painful engorgement of the breasts in 87.3 per cent of 55 nonnursing mothers. A delayed transitory heaviness or filling of the breasts, usually painless, was noted in 20 of these cases anywhere from the fifth to eleventh post-partum day. In dosages of 100 to 200 mg., it acted as an excellent "priming" agent for the uterus in 80 per cent of the cases where one or more previous medical inductions of labor, including pituitrin, had been unsuccessful. Used alone, without oxytocics, stilbestrol did not precipitate labor.

The pregnant and puerperal patient is remarkably tolerant of stilbestrol in doses from 250 mg. a day to 1,500 mg. a week. No toxic effects were noted even in patients with eclampsia or fulminating toxemia and evident renal and liver damage. In the management of the patient suffering from a menopausal syndrome, the drug, where indicated, is an effective adjuvant in controlling the vasomotor phenomena.

intermuscular connective tissue. Therefore, the uterus increases in size and the cavity enlarges. During the menstrual cycle there is no effect on the uterus as regards contractions even when large doses are given. Pituitary extract produces an increased pressure within the uterus only after estrogen has been secreted in the body, namely, at the time of menstruation. In some cases there is a reverse reaction; that is, pituitary extract produces a fall in intrauterine pressure.

The pregnant uterus does not react to administration of estrogen or of follicle hormone in the form of pregnancy serum; hence pregnancy cannot be disturbed in this way. Uterine contractions begin only when the increase in length of the muscle fibers and the increase in connective tissue ceases. The posterior pituitary hormone then induces uterine contractions to produce increased intrauterine pressure.

The growth impulse of the uterus during pregnancy comes from the follicle hormone which is formed in the placenta. The increased output of estrogen toward the end of pregnancy is indicative of the removal of this hormone which now becomes superfluous and must be removed in order to permit the uterus to react to the posterior pituitary hormone so that labor may begin.

During pregnancy the uterus is prevented from reacting by the inhibiting action of the corpus luteum hormone and the gonadotropic chorionic hormone.

J. P. GREENHILL

**Hoffmann, Fr., and Treite, P.: Influence of Follicle Hormone on Bladder Capacity, Zentralbl. f. Gynäk. 65: 783, 1941.**

Hoffmann administered 5 to 10 mg. of estradiol to a group of women in premenopausal and climacteric ages who were suffering from frequency of urination and incontinence with atonic bladders. The average bladder capacity was determined prior to medication and three, five, and twelve days after medication. Subjective relief was experienced in varying degree in all cases and a maximum diminution in bladder capacity was noted three days after medication, slowly increasing to the twelfth day. Reductions for the series ranged from 27 to 45 per cent, average 35.

R. J. WEISSMAN

**Guirdham, A.: Sex Hormones and Blood Pressure, Bristol Med.-Chir. J. 58: 19, 1941.**

The author quotes Simpson and Schaefer who indicate that estrogens favorably affect menopausal hypertension and that testosterone, by a stabilizing effect on sympathetic-parasympathetic balance, can either raise or lower blood pressure in the absence of hyperpiesis due to organic disease. Two interesting cases are cited. (1) A 78-year-old woman with a pressure of 220/120, gross arterial degeneration and enlarged left ventricle was given 0.14 mg. of estradiol daily by inunction, resulting in reduction of pressure to 150/70 in two weeks with improvement in mental condition (depression). (2) A 53-year-old patient with melancholia, arteriosclerosis, myocarditis, poor peripheral circulation, and a pressure of 164/84 was given 0.28 mg. of estradiol ointment daily, increased in 14 days to 0.56 mg. In nineteen days marked mental improvement and reduction of pressure to 105/65 occurred. The dose was reduced to 0.56 mg. every other day for one month, with great subjective mental and physical improvement, and pressure was 96/60. The medication was omitted for one month and pressure rose to 108/60 in thirty days. Now inunction with testosterone, 2 mg. daily, raised pressure to 130/70. Patient appeared brighter and more dynamic. The dose was raised to 4 mg. and in four days the pressure was 148/70.

R. J. WEISSMAN

production in pregnant and nonpregnant women. He does not believe that the pregnanediol excretion rate provides a reliable estimate of the intensity of corpus luteum metabolism. The great discrepancy between the relatively large amounts of pregnanediol recovered after progesterone injection by Venning and Browne and the failure to recover any by Hamblen, Ashley and Baptist and by Stover and Pratt together with Cope's intermediate recoveries suggests to him that other factors, undefined, are concerned in determining the pregnanediol excretion from a given quantity of progesterone. If this is probable after injection of progesterone, it may be equally probable for endogenous progesterone. He believes that hormone influences other than renal or hepatic and the metabolic state of the uterus and endometrium will be proved important in progesterone metabolism and pregnanediol excretion. The assumption that pregnanediol excretion reflects quantitative variations in corpus luteum activity is unsupported by direct evidence.

J. P. GREENHILL

Quintela, F.: **Factors Affecting Intersexuality**, Rev. méd. munic. Rio de Janeiro 1: 783, 1941.

The author gives an extended and complete discussion of chromosomal factors affecting sexuality and cites an interesting case of intersexuality in a woman of male skeletal structure with a greatly enlarged clitoris which resembled the male organ in many respects, including urinary meatus. Quintela concludes that in spite of extensive overlapping in many individual cases three general morphologic and physiologic groups may be defined: First, a very early inversion with arrest of gonad cortex growth and overgrowth of medullary tissue. This is associated with growth of Wolffian ducts and male type internal genitals. Second, a midway inversion in which there is little cortical gonad differentiation of male elements (ovotestis). Here growth of uterus and tubes is at a standstill; Wolffian canal is moderately well developed. The third and ultimate stage of this process shows the ovary well developed but with little cortical potentiality. Microscopically an involutional type of structure is seen. The uterus is small, tubes infantile, Wolffian remnants more or less well developed.

Sexuality, says the author, is first presaged by chromosomal factors, second by embryonic "cortixin" and "medullarin" of the gonads. Finally the fully developed gonad elaborates the true gonadal hormones of adult life.

R. J. WEISSMAN

Lipschutz, Alexander, and Vargas, Luis: **Prevention of Experimental Fibroids by a Cortical Hormone**, Lancet 1: 568, 1941.

Further studies of the tumorigenic action of estrogenic substances in the guinea pig reveal that the acetic ester of desoxycorticosterone completely prevents the development of uterine fibroids and reduces the production of extra genital fibroids to a minimum. Extreme development of the uterus and uterine bleeding were also inhibited. The amount of desoxycorticosterone necessary to inhibit tumorigenic activity is about three times the amount of estradiol necessary to produce tumors. In this action it is superior to testosterone and progesterone.

CARL P. HUBER

Kneer M.: **Effect of Follicle Hormone on the Function of the Human Uterine Musculature**, Arch. f. Gynäk. 170: 483, 1940.

The investigations showed that the follicle hormone stimulates growth of the muscle fibers of the human uterus and also produces an increase and loosening of the

control of cyclic ovarian function in large measures still awaits commercial production of the two pituitary hormones in separate form. But even then the practical difficulty will remain to duplicate the continuously varying amounts of gonadotropins flowing into the blood stream. Efforts could be made to control the gonadotropin output of the pituitary by administration of estrogen and progestin but also the natural ebb and flow would still remain as essential requirement. These complexities are Nature's doings and must be faced.

It is true that any of the four hormones can be given arbitrarily in any dose desired, and may by good luck restore normality. The best that can be hoped for by any system of constant dosage is the substitution of one abnormal condition for another. It may or may not be better than the abnormality it supersedes. It sometimes is better and the patient secures relief.

Only in the menopause current therapeutic practice comports adequately with physiologic principles.

Another striking fact, which the practical therapist conventionally ignores, is that women produce nearly as much male sex hormone as men. It is possible that this paradoxical arrangement is meaningful and that the therapist may have to reckon with it before his results can become satisfactory to him or his patient. Another theoretical, if not practical, complication of gynecic endocrinology is that the adrenal cortex is able to produce sex hormones, both estrogens and androgens. What part the adrenal glands may play in cyclic sex activities of normal women is still completely unknown.

An additional hormone with considerable influence on reproductive processes is prolactin. It is unknown whether aberrations of prolactin might possibly be of significance for menstrual disorders.

There is not now and probably never will be any effective easy way to practice gynecology by using endocrine therapy.

HUGO EHRENFEST

Stemmer, W.: *The Vegetative Effects of Semen on the Female Organism*, Zentralbl. f. Gynäk. 64: 1528, 1940.

Stemmer has made an almost encyclopedic study of the influences attributed to seminal absorption from writers like Hippocrates, who observed that women having regular sexual intercourse were healthier, to date. The author concludes that a good deal of absorption takes place from the seminal pool and that substances of biologic nature similar to male hormone are deposited in the semen and have various effects upon the woman. A sort of postcoital endometritis has been noted by some workers quoted by Stemmer and he believes that this leucocytic response to the presence of semen on the endometrium is one of the prime factors in the growth of the hypoplastic uterus which is often noted in married women. Sexual intercourse results in mobilization of thyroxin in the individual; the increased metabolism resulting allows greater absorption of seminal components. The author notes in contrast the altered clinical and serologic findings in women practicing masturbation, coitus interruptus, or using chemical means of contraception. As added evidence of the influence of seminal factors, the author cites the difference in color of fertilized and unfertilized eggs, in some species of Aves, and the additional fact that some species of animals even during pregnancy have a period of receptivity to the male.

R. J. WEISSMAN

Bompard, E.: *Treatment of Uterine Functional Hemorrhages by the Male Hormone*, Rev. franc. de gynéc. et d'obst. 36: 77, 1941.

The author maintains that functional uterine hemorrhages can be cured or relieved in nearly all cases by injections of testosterone. This therapy has changed the man-

**Hoepfner Dutra, L.: Opothepy and Hormone Therapy in Menopause, An. brasil. de Ginec. 9: 395, 1940.**

In a case of surgical menopause the author observed vaginal changes in biopsy and smear as affected by oral administration of whole ovary in large doses, folliculin and stilbestrol. Although some changes were noted following whole ovary medication, folliculin and stilbestrol produced more pronounced and longer lasting effects.

R. J. WEISSMAN

**Ottoway, John P.: The Correlation of Vaginal Smear Changes in the Estrogenic Treatment of Menopausal Symptoms and Senile Vaginitis, Harper Hosp. Bull. 1: 29, 1941.**

Twenty-eight patients with menopausal symptoms were studied by the vaginal smear method. The initial vaginal smears before treatment indicated an advanced or moderate estrogenic deficiency in 10 patients. Eleven showed slight deficiency and seven presented normal Grade 4 smears. Treatment consisted of weekly or semi-weekly injections of estradiol varying from 1,000 to 10,000 rat units per injection. Two patients were slightly relieved, 18 partially relieved, and 8 entirely relieved. Objective improvement as recorded by the vaginal smears was seen in only 14 of the 28 patients. Only 6 progressed from a deficient type to a normal Group 4.

Ten patients were treated for senile vaginitis. Initial smears revealed moderate or advanced estrogenic deficiency in 7 cases, and the remaining 3 showed slight but definite deficiency. Treatment consisted of the daily local application of estradiol in vaginal suppository form, the dosage varying from 480 to 4,800 rat units per suppository. Progressive improvement in the vaginal smear was obtained in 6 patients. The remaining 4 cases showed little change in the smears, and there was little or no improvement in the vaginitis.

WILLIAM BERMAN

**Hoskins, Roy G.: The Current Status of Female Sex Hormones, New England J. Med. 225: 722, 1941.**

Quite recently, an eminent gynecologist, who had himself made important contributions to this problem stated in effect that, except for a certain amount of amelioration of the discomforts of the menopause, gynecic endocrinology had contributed practically nothing to the welfare of women. "The condemnation was no doubt too sweeping, but it serves to raise the question why the discoveries of the investigators have failed to yield more substantial clinical returns." It is the aim of the writer to consider basic advances in information concerning sexual physiology of women and to suggest certain possibilities for the extension of clinical research, with the idea of making the physiologic discoveries more fruitful.

In consequence of a double reciprocating arrangement, on every day of the month, four important hormones (luteinizing, progestin, follicle stimulating, and estrogen) are normally present in different absolute amounts, as well as in different proportions of one to another. Only by this precise and constantly shifting system of checks and balances is the normal menstrual cycle maintained. Any serious dislocation of this fourfold balance spells menstrual disorder. Without taking these fundamental facts fully into account actual restoration to normality cannot be obtained.

Pituitary gonadotropins as at present available are probably not worth using. It has become possible to separate the follicle-stimulating from the luteinizing pituitary hormone, but the yield is small, and "these two hormones are consequently too expensive for the use of anyone but investigators and millionaires." The mare serum gonadotropin was formerly believed to give pure follicle stimulation, but as recently shown it also influences corpus luteum formation. Successful therapeutic



its use is indicated and if the corpus luteum of pregnancy should be removed at operation and maintenance of pregnancy is desired, administration of the hormone should be begun simultaneously with the operation if not sooner.

R. J. WEISSMAN

**Hamblen, E. C., and Pullen, R. L.: The Endocrine Therapy of Ovarian Failure, Virginia Med. Monthly 68: 375, 1941.**

Rational therapy of ovarian failure is dependent upon the establishment of a correct diagnosis, the degree and the nature of the ovarian impairment, and the segregation of the etiologic factors underlying the ovarian failure. There are three established symptoms and signs of marked ovarian failure: one, failure of occurrence or cessation of menstruation; two, nonoccurrence of sexual maturation, or regressional changes in the sex organs; three, impaired fertility or sterility. Ovarian failure may be either of the corpus luteum (failure of ovulation) or estrogenic variety. The causes of ovarian failure fall into two general groups: one, extraendocrine, and two, endocrine causes. In the former are included acute and chronic debilitating diseases, vitamin deficiencies, emotional and psychic disturbances, etc. The alterations in ovarian function are likely attributable to indirect effects on the pituitary-ovarian axis mediated via the pituitary gland. The endocrine causes of ovarian failure include intrinsic ovarian failure, hypofunction of the pituitary, diseases of the adrenal and thyroid glands, endometriopathic factors, and gametopathic factors.

There are three general indications for the endocrine therapy of ovarian failure per se: (1) completion of sexual development in adolescent failure; (2) therapy of undesired sterility in adult failure; and (3) treatment of irregularities of uterine bleeding. In adolescent failure, gonadotropic hormone in the form of equine gonadotropin in doses of 400 to 800 I.U. every two days for a period of six weeks, followed by a second series after a rest period of six weeks, is indicated. If no response is obtained it may be assumed that no pituitary deficiency exists. Substitutional ovarian therapy is then indicated. The authors advise the use of 1 to 2.5 mg. of estradiol benzoate or estradiol dipropionate every two or three days until there is genital response. In adult ovarian failure before the menopause, the authors advise the cyclic employment of estrogen-progesterone therapy, using 0.3 mg. of estradiol benzoate every two days for a period of ten days followed by 0.3 mg. of estradiol benzoate and 5.0 mg. of progesterone every other day for ten days. If no response is obtained, as shown by endometrial scrapings, after two such series of cases estradiol benzoate and progesterone are given simultaneously during the latter half of the menstrual cycle. The authors do not give the results of their treatment.

EUGENE S. AUER

**Sievers, K., and Schenz, H.: Experiments to Determine Follicle Hormone Effect on Uterine Activity, Zentralbl. f. Gynäk. 64: 1522, 1940.**

The authors wished to determine whether the increased follicle hormone in circulation at the end of pregnancy had any influence upon uterine tonus or activity. Castrated dogs, in their experiments, showed no response to the administration of pituitrin when follicle hormone had been intravenously administered previously. The same animals, however, showed a good response to pituitrin when estradiol had been given at least one week previously. They conclude that a direct stimulating or tonic effect of follicle hormone was not demonstrated.

R. J. WEISSMAN

agement of functional uterine bleeding by considerably reducing the incidence of curettement and radiation therapy. The acetate and propionate have identical effects. In most cases of premenstrual bleeding from 50 to 200 mg. usually suffice. However, in serious cases of bleeding a cure cannot be obtained unless from 300 to 800 mg. of testosterone are given during a period of three to four weeks. Following this it is necessary to give from 50 to 200 mg. during each of the next two or three months. The usual results of this therapy are amenorrhea for a few months and atrophy of the endometrium. These results are not objectionable because the effects of testosterone are temporary.

J. P. GREENHILL

**Ehrhardt, K.: Clinical Experiments on Pregnancy Maintaining Effect of Corpus Luteum Hormone After Loss of Corpus Luteum of Pregnancy, Zentralbl. f. Gynäk. 65: 541, 1941.**

The author removed the corpus luteum of pregnancy during abdominal sterilization of women whose pregnancy was to be interrupted for medical or eugenic reasons and administered varying doses of corpus luteum hormone, to determine optimal dosage for maintenance of pregnancy. In the experiments with mice fetal death occurred after large doses of corpus luteum hormone. Somewhat smaller doses resulted in retention, maceration, and resorption of uterine contents. In the same animal, however, live, dead, macerated, and resorbing fetuses could be seen. Doses of 5 Corner units or more resulted in death of all fetuses; 2.5 to 5 units resulted in partly live and partly dead litters but part of the living offspring died in the neonatal period, possibly due to poor suckling as well as previous intrauterine injury. Similar results were obtained with guinea pigs.

The corpus luteum of pregnancy is said to be most active during the first trimester, then beginning retrogression. Ehrhardt and others determined the corpus luteum hormone content of the young placenta was negligible, activity beginning in the fourth to fifth month and at its best during the sixth or eighth month. The mature or term placenta has relatively low and inconstant amounts of corpus luteum hormone. The author feels that habitual abortion is prone to occur during the third month while the corpus luteum of pregnancy is losing its function and the placenta is beginning to take over corpus luteum hormone production. Since no damage has resulted to pregnancy in clinical work with doses of up to 1400 mg. of corpus luteum hormone, the possibility of overdosage appears small. Some workers have felt that administration of corpus luteum hormone in threatened abortion increased bleeding and contractility of the uterus, but where the products expelled have been examined with care pathologic ova have generally been found. The author cites several cases of removal of corpus luteum of pregnancy: This was done in a 35-year-old patient who was two and one-half months pregnant. Fourteen hundred mg. of corpus luteum hormone was administered over the first 16 postoperative days. Two attempts at medical induction and a fall downstairs did not affect the fetus. Vaginal induction thirty-seven days after operation resulted in expulsion of a live 16 cm. fetus. The operation was performed on a 40-year-old woman two and one-fourth months pregnant. She received 400 mg. corpus luteum hormone over the first 11 postoperative days followed by two futile attempts at medical induction. Vaginal induction twenty-two days postoperatively resulted in expulsion of a live 12 cm. fetus. A 33-year-old woman two and one-half months pregnant received 260 mg. of corpus luteum hormone after removal of the corpus luteum. Two unsuccessful medical inductions were followed by expulsion of a live 15 cm. fetus after vaginal induction on the twenty-second postoperative day. The author also cites a case of habitual abortion in which pregnancy was successfully carried to term after corpus luteum hormone had been administered in the interval between impregnation and implantation of the ovum. The author concludes that corpus luteum hormone should be given in large doses where

## Correspondence

### Vitamin C Deficiency as a Possible Factor in the Pathogenesis of Erythroblastosis Fetalis

*To the Editor:*

The increasing attention which is being given to iso-immunization during pregnancy by the Rh factor with its extreme danger of transfusion accident in the mother (Burnham, L.: *AM. J. OBST. & GYN.* 42: 389, 1941) and high mortality rate in the baby (erythroblastosis) necessarily should include a search for any etiologic agent which may permit iso-immunization. I am prompted therefore to submit for consideration a possible explanation for the transfer of blood from the fetal circulation to the maternal circulation. This transfer has been assumed to occur, thereby leading to iso-immunization of the mother and resulting in the various manifestations of erythroblastosis in the baby in the following manner:

Since the Rh factor occurs in the red blood cells and is probably limited to them, it has been assumed by Levine (Levine, P., Burnham, L., Katzin, E. M., and Vogel, P.: *AM. J. OBST. & GYN.* 42: 925, 1941) that red blood cells of the fetus must pass through the capillaries and epithelium of the chorionic villi into the intervillous spaces and thus into the mother's blood stream in sufficient numbers to induce immunization. Subsequently intervillous hemorrhages of fetal blood within the placentas of patients who have delivered erythroblastic babies were described by Javert. (Javert, C. T.: *AM. J. OBST. & GYN.* 43: 921, 1942. Also personal communication to the author.) This provides evidence of the escape of fetal blood into the maternal circulation, resulting in immunization of the mother by the Rh factor and the formation of anti-Rh agglutinins in the mother's serum. These agglutinins, in common with other antibodies, are then free to pass through the placental barrier into the fetus where they agglutinate and destroy its blood, thus causing erythroblastosis. In addition, if the mother be transfused with blood containing the Rh factor, these agglutinins are free to agglutinate and destroy the transfused red blood cells causing jaundice and transfusion anuria.

I believe that a vitamin deficiency in the mother must be considered as a possible factor in the passage of fetal blood through the tissues of the chorionic villus. It is well known that vitamin C is not stored in the body, thus necessitating a daily intake and, that a deficiency of vitamin C causes damage to the endothelium of blood vessels. It seems logical to expect that this damaging effect would be more pronounced on the newly forming and formed capillaries of the chorionic villi than on the well-developed capillaries of the adult. Thus a subclinical deficiency of vitamin C in the mother might be sufficient to permit a break in the integrity of the capillaries of the chorion with the escape of fetal blood.

Dalldorf (Dalldorf, G.: *Am. J. Dis. Child.* 46: 794, 1933) has shown a definite relationship between the vitamin C value of the food and the resistance of the capillary and walls. The escape of blood from capillaries with the resultant formation of petechiae occurred more readily when there was a shortage of vitamin C. This was true even when the deficiency was not sufficient for the development of manifest scurvy.

Likewise, Hess (Hess, A. F.: *Scurvy, Past and Present*, Philadelphia, J. B. Lippincott Co.) has pointed out that children exhibiting symptoms of irritability, lack of stamina, and retardation of growth can be cured by increasing the amount of vitamin C in the diet even though the diet has been sufficient to prevent scurvy.

Hence it seems possible that a relative deficiency of vitamin C existing over a shorter or longer period of pregnancy would be sufficient to allow fetal blood to pass through the chorion with iso-immunization resulting. Many pregnant women

Bennett, M. J., and Russell, P. B.: *Vaginal Smears Correlated to Ovarian Function (Four and One-Half Months' Fetus Through Puberty)*, South. Surgeon 10: 79, 1941.

The examination of daily vaginal smears is a valuable aid in the diagnosis of ovarian dysfunctions when correlated with biologic assays, blood chemistry determinations, and other studies. Indications for therapy are based upon the information obtained.

Cyclic changes occur in the vaginal mucosa which indicate either follicular or luteal stimulation, and they represent the anaphase and cataphase of ovarian activity, respectively. Each is characterized in the smear by a typical cytologic and bacteriologic appearance. Vaginal smears of a woman at the eighteenth week of pregnancy revealed evidence of luteal domination, while vaginal smears of her fetus at this period of gestation indicated follicular stimulation. This is interpreted as signifying that function of the fetal ovaries has commenced, and that they are independent of maternal influence. At twenty-eight weeks' gestation, both the maternal and fetal vaginal smears show predominance of follicular stimulation, while on the day of full term the same reaction is present. Vaginal smear evidence of the follicular phase persists in the full-term infant until approximately its ninety-fourth day of life. Hormone stimulation of the maternal milk upon the nursing infant's ovaries is negligible.

The authors make the statement that: "It seems an easy matter to predict the cycle of the mature female and diagnose abnormal ovarian conditions by studying the vaginal smears of the young female previous to the onset of the menses or puberty."

ARNOLD GOLDBERGER

Pardini, Icilio: *The Hormonal Content of Parovarian Cystic Fluid Removed During Pregnancy*, La Ginecologia 19: (Series 2) 187, 1941.

The author reports his findings from four Friedman tests performed with cystic fluid aspirated from parovarian cysts. The tumors, from which the cystic fluid was obtained, were removed by laparotomies upon four patients. All of these patients were pregnant at the time of their operations. Two women were in their second month of pregnancy, one case was six months pregnant, while the last case was at term at the time of her surgery.

All four of the Friedman tests were reported negative. The uteri and ovaries of each of the test animals were examined by laparotomy prior to their use as test animals. A total of 24 to 32 c.c. of cystic fluid from the parovarian tumors were used in each test animal. Each animal received a 6 to 8 c.c. intravenous injection of the cystic fluid in its ear veins on four occasions.

The author concludes with the theory that the pathologic changes in the capsule of the ovarian cyst precluded interexchange of tissue fluids between that within the tumor and that in the body. Inasmuch as the fluid in the cystic tumors was antecedent to pregnancy, it followed that the Friedman pregnancy test done with the tumor liquid would be negative, as it proved to be.

CLAIR E. FOLSOME

# Announcement

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## A Registry of Ovarian Tumors

At its recent annual meeting the American Gynecological Society undertook the sponsorship of an *American Registry of Ovarian Tumors*, and appointed from its Fellows a committee of five gynecologic pathologists to carry on this work.

The need and wisdom of such a project must be obvious to every gynecologist, for no problem of pathology is in greater need of clarification. No entirely satisfactory classification of ovarian tumors exists, largely because of our ignorance of the histogenesis of many of these growths. Even in tumor types which are fairly well defined, such as the papillary growths, prognosis is often difficult, because of the not infrequent lack of parallelism between clinical and histologic malignancy, and mistakes in both diagnosis and prognosis are frequent. Again, tumors are not infrequently encountered concerning the nature of which even expert pathologists cannot be certain. Finally, a whole group of ovarian tumors of rather special histogenesis and histology has been described in recent years, and there are many pathologists who, because of the relative rarity of these tumors, have had no opportunity of familiarizing themselves with their histologic characteristics.

Instead of limiting its study to a registry of rare ovarian tumors, comparable perhaps to that which has been employed so successfully by general pathologists with bone sarcoma, the committee has decided to widen its scope to include ovarian tumors of all varieties. It therefore seeks the cooperation of all gynecologists and pathologists in this ambitious project, and appeals to them for cooperation by seeing to it that properly prepared slides of all ovarian tumors, more particularly those of unusual or doubtful nature, be sent to this central registry for composite study by the members of the committee.

With the slides should be sent an adequate clinical history, including such essential data as the patient's age, menstrual and marital history, gynecologic findings, and the operative procedure carried out, as well as a gross description of the tumor. Where photographs of the latter are available, they would be welcome. If the gross specimen or blocks of tissue are sent, they should be fixed in 10 per cent formalin.

It is obvious that the real value of such a study would be enormously lessened if it did not include also a study of the subsequent course of the patients, particularly in the malignant and doubtful groups of tumors. Such correlated clinical and histologic study must be the chief hope of improving our evaluation and classification of ovarian neoplasms. To facilitate such a follow-up study the name of the attending surgeon should be included in the data.

The Committee has no intention of making this a purely diagnostic service, but all those who send in slides will in due course receive reports of the diagnosis and classification arrived at by the Committee. Since each slide will be studied by every member of the Committee, and perhaps by other pathologists as well, and since this will involve corre-

have nausea and vomiting during the early months of pregnancy and not infrequently these disturbances of the gastrointestinal tract persist throughout long periods of pregnancy, thus interfering with the ingestion of fruits and fruit juices. In addition some patients have food habits and tastes which make adequate vitamin C intake unlikely, while others state that they cannot eat fruits or fruit juices because of indigestion.

The history of one of the most recent cases of immunization (Case C. M. M.) was investigated from this standpoint. It was so suggestive that this patient may have had a pronounced vitamin C deficiency over a long period of her pregnancy that a few other recent cases were investigated together with two previously reported cases (J. L. and H. H.).

Ten Rh negative mothers of erythroblastic babies have been carefully questioned as to their diet during pregnancy. Nine of the ten have histories very suggestive of vitamin C deficiency in the diet during at least some appreciable part of their pregnancies and none of these nine took any capsules containing vitamin C at any time. The tenth patient took a large number of multivitamin capsules as well as a diet containing plenty of vitamin C and yet delivered an erythroblastic baby. This apparent exception might still be explained on a failure of assimilation of vitamin C from the intestinal tract even though the intake was ample.

An eleventh patient should be mentioned because she took a large amount of vitamin C throughout her pregnancy and delivered an apparently normal baby when an erythroblastic baby was to have been expected.

This last patient (H. H.), who was the first in whom the anti-Rh agglutinins were ever identified, was delivered two years ago of an apparently normal baby in spite of the demonstrable presence of the anti-Rh agglutinins in her serum. These agglutinins are proof that the process of immunization has taken place, and up to this time it has been a puzzle as to why the baby was apparently not affected. The fact that this patient was instructed to take orange or other fruit juice every day and took Abdol with vitamin C capsules twice daily starting at the seventh week, now offers a possible explanation, i.e., that the immunization occurred during previous pregnancies, three of which ended in early or late spontaneous abortions. It is interesting to note that weak anti-Rh agglutinins are still demonstrable in her serum two years after her last (normal) pregnancy.

These 11 cases, with the one exception, are mentioned as suggestive evidence in support of the hypothesis of vitamin C deficiency in the role of iso-immunization. Vitamin C determinations during all stages of pregnancy and detailed examination of the placentas to corroborate the finding of intervillous hemorrhages are now being carried on in an effort to prove or disprove this hypothesis.

The hypothesis that vitamin C deficiency during pregnancy permits fetal red blood cells to escape into the maternal circulation, thus leading to iso-immunization of the mother by the Rh factor, and resulting in the various manifestations of erythroblastosis in the baby, is submitted for consideration.

The prevention of iso-immunization and erythroblastosis may therefore depend upon daily adequate vitamin C intake by the mother.

It is suggested that all pregnant patients be given adequate vitamin C daily starting as early in pregnancy as possible; and that those patients who have been or may be subject to iso-immunization (erythroblastosis fetalis) be given large amounts of vitamin C every day (by injection if necessary).

The patients who may be subject to immunization include all Rh negative women with Rh positive husbands, especially those who have delivered erythroblastic babies, as well as those untested women who have had an unexplained macerated fetus, stillbirth, neonatal death or late abortion.

LYMAN BURNHAM, M.D.

229 ENGLE STREET  
ENGLEWOOD, N. J.  
AUGUST 12, 1942

The Part II examination for this year will be held at Pittsburgh, Pa., beginning Wednesday, May 19, and closing Tuesday, May 25, 1943.

If a candidate in Service finds it impossible to proceed with the examinations of the Board, deferment without time penalty will be granted under a waiver of our published regulations covering civilian candidates.

Candidates for re-examination in this year's Part I must request such re-examination before December 15, 1942.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

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## Central Association of Obstetricians and Gynecologists

By a decisive vote of the membership, the annual meetings of this Association have been suspended for the duration of the War.

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## American College of Surgeons

The 1942 Clinical Congress of the American College of Surgeons, originally scheduled for October at the Stevens Hotel, Chicago, which was taken over August 1 by the United States Army Air Corps, will be held in Cleveland, with headquarters at the Cleveland Public Auditorium, from November 17 to 20, 1942. The twenty-fifth annual Hospital Standardization Conference sponsored by the College will be held simultaneously.

The program of panel discussions, clinical conferences, scientific sessions, hospital meetings, and medical motion picture exhibitions at headquarters, and operative clinics and demonstrations in the local hospitals and Western Reserve University School of Medicine, has been centered around the many medical and surgical problems arising out of the prosecution of an all-out effort to win the war, emphasizing the needs of the rapidly expanding medical services of the Army and the Navy, and consideration of special problems related to the increasing activities for civilian defense.

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## Books Received

**SEX FULFILLMENT IN MARRIAGE.** By Ernest R. Groves, Professor of Sociology, University of North Carolina, Gladys Hoagland Groves, and Catherine Groves. Introduction by Robert A. Ross, M.D., Associate Professor of Obstetrics and Gynecology, Duke University, School of Medicine. Illustrated (by Robert L. Dickinson, M.D.), 319 pages. Emerson Books, Inc., New York, 1942.

**MARRIED LIFE IN AN AFRICAN TRIBE.** By I. Schapera, Professor of Social Anthropology in the University of Capetown. With an introduction by Bronislaw Malinowski. Illustrated. 364 pages. Sheridan House, New York, 1942.

**GLANDULAR PHYSIOLOGY AND THERAPY.** A Symposium, prepared under the auspices of the Council on Pharmacy and Chemistry of the American Medical Association. American Medical Association, Chicago, 1942.

**BLOOD GROUPING TECHNIC.** By Fritz Schiff, M.D., Late Chief of Department of Bacteriology, Beth Israel Hospital, and William C. Boyd, M.D., Associate Professor of Biochemistry, Boston University School of Medicine, etc. With a Foreword by Karl Landsteiner, Rockefeller Institute for Medical Research. 248 pages. Interscience Publishers, Inc., 215 Fourth Ave., New York, 1942.

**WAR GASES. Their Identification and Decontamination.** By Morris B. Jacobs, Ph.D., formerly Lt. U. S. Chemical Warfare Service Reserve. 180 pages. Interscience Publishers, New York, 1942.

spondence between men scattered in different sections of the country, it will be understood that such reports of findings cannot be made with great promptness.

Finally, the Committee fully appreciates that many of the ovarian tumors submitted to it will be worthy of report by the referring physicians, and it need scarcely emphasize that neither the Committee as a whole, nor any individual member thereof, will utilize any submitted case for publication without the express permission of the referring physician. It is hoped that, as the work progresses, reports of the Committee's studies will be published from time to time, but those referring cases for study will be given full credit in any such publication.

The Committee feels that it has been given a great opportunity to render a worth-while service and it sincerely hopes that individual clinicians and pathologists in all sections of the country will feel that they too can contribute vitally in this project, by developing the routine of sending slides of interesting ovarian tumors, with the above indicated data, to the committee for study and registry. This material should be mailed to Dr. Emil Novak, Laboratory of Gynecological Pathology, Johns Hopkins Hospital, Baltimore, Md.

EMIL NOVAK, CHAIRMAN  
ROBERT MEYER  
HERBERT F. TRAUT  
GEORGE H. GARDNER  
KARL MARTZLOFF

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## Items

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### American Board of Obstetrics and Gynecology

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Saturday, February 13, 1943, at 2:00 P.M.

Arrangements will be made so far as possible for candidates in military service to take the Part I examination (written paper and submission of case records) at their places of duty, the written examination to be proctored by the Commanding Officer (medical) or some responsible person designated by him. Material for the written examination will be sent to the proctor several weeks in advance of the examination date. Case records may be submitted in advance of the above date, only by candidates in Service, by forwarding these to the office of the Board Secretary by the candidate upon entering military service, or in the event of assignment to foreign duty. All other candidates should present their case records to the examiner at the time and place of taking the written examination.

The Office of the Surgeon-General (U. S. Army) has issued instructions that men in Service, eligible for Board examinations, be encouraged to apply and that they may be ordered to "Detached Duty" for the purpose of taking these examinations whenever possible. The Office of the Surgeon-General of the U. S. Navy presumably takes a similar attitude on this matter.

All candidates will be required to take both the Part I examination, and the Part II examination (oral-clinical and pathology examination). Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held later in the year.



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# AMERICAN JOURNAL

OF UNIVERSITY OF WASHINGTON  
SCHOOL OF NURSING  
HARBORVIEW DIVISION

# OBSTETRICS AND GYNECOLOGY

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TABLE OF CONTENTS ON PAGE 6

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## CONTENTS FOR DECEMBER, 1942

### AMERICAN GYNECOLOGICAL SOCIETY

SIXTY-SEVENTH ANNUAL MEETING, JUNE 15 to 17, 1942

(Concluded)

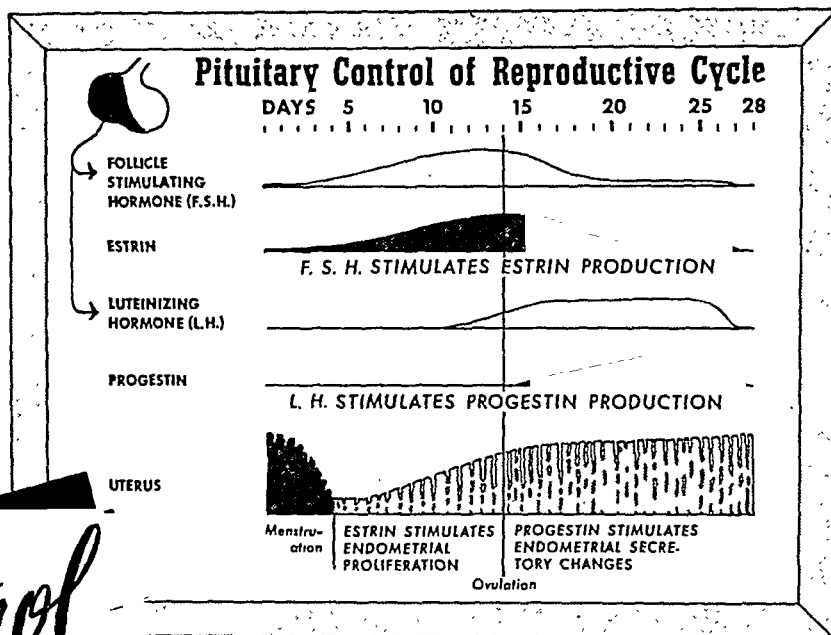
|   |      |
|---|------|
| Malignancy Subsequent to Irradiation of the Uterus for Benign Conditions. Lewis C. Scheffey, M.D., Philadelphia, Pa. ....   | 925  |
| The Functional Anatomy of Labor, With Special Reference to the Human Being. A. C. Ivy, Ph.D., M.D., Chicago, Ill. ....  | 952  |
| Some Aspects of Early Human Development. John Rock, M.D., and Arthur T. Hertig, M.D., Boston, Mass. ....  | 973  |
| The Effect of Progesterone in Adolescent Girls and Young Women With Functional Uterine Bleeding. Willard M. Allen, M.D., St. Louis, Mo., and George P. Heckel, M.D., Rochester, N. Y. ... | 984  |
| The Experience of the Johns Hopkins Hospital With Cesarean Section. C. P. Manahan, M.D., H. F. Connally, Jr., M.D., and N. J. Eastman, M.D., Baltimore, Md. ....                          | 999  |
| The Possible Etiologic Role of Gynecologic Lesions in the Production of Hypertension. Houston S. Everett, M.D., and Roger B. Scott, M.D., Baltimore, Md. ....                             | 1010 |
| Gonorrhea in the Female and Its Treatment With Sulfonamides. R. Gordon Douglas, M.D., Iona F. Davis, and James F. Shandorf, M.D., New York, N. Y. ....                                    | 1026 |
| Studies of the Human Corpus Luteum. John I. Brewer, M.D., Ph.D., Chicago, Ill. ....   | 1048 |
| Partial Congenital Aplasia of the Vagina. Walter T. Dannreuther, M.D., F.A.C.S., New York, N. Y. ....   | 1063 |
| A Bacteriologic Study of Pyometra. Bayard Carter, M.D., Durham, N. C. ....  | 1074 |
| The Experimental Production of Toxemia of Pregnancy. Franklin F. Snyder, M.D., Chicago, Ill. ....   | 1091 |
| Selective Hysterectomy for Nonmalignant Uterine Disease. Edward G. Waters, M.D., F.A.C.S., Jersey City, N. J. ....  | 1107 |

### Items

|  |      |
|--|------|
| American Board of Obstetrics and Gynecology..... | 1118 |
| American College of Surgeons.....                | 1118 |

### Index

|             |      |
|-------------|------|
| Index ..... | 1119 |
|-------------|------|



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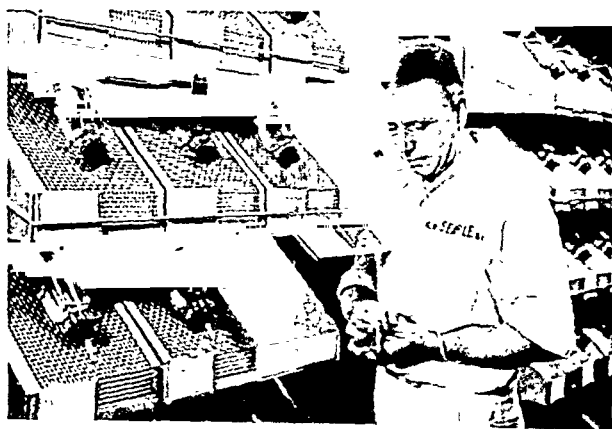
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references may have been overlooked. The site of the malignancy was cervical in 18, fundal in 40, and not mentioned in 13.

To this total, we now add 20 additional cases, with accompanying data and appropriate comment. The first group comprises 7 patients with cervical carcinoma and the second includes 12 patients with fundal carcinoma and one with myosarcoma.

To justify a contribution such as this, it is necessary to furnish factual evidence of practical value and to determine whether or not certain factors influence the subject at issue. This cannot be done by creating hypotheses, but only by a critical evaluation of the evidence presented in each particular case.

Certain pertinent questions naturally arise at the outset of this investigation. They may be summarized to some extent as follows:

1. What type of benign lesions were subjected to irradiation therapy and what other procedures accompanied it?
2. Was an irradiation menopause produced?
3. What time intervened between the treatment for the benign condition and the discovery of malignancy?
4. In what location was the subsequent malignancy found, what was the extent of the lesion, what did the histopathology reveal, and was the grade of malignancy of any particular significance with respect to the final outcome?
5. Might malignancy have been present at the time of the primary treatment and overlooked because of errors of omission?
6. Was there any reason to believe that the irradiation therapy either retarded or accelerated the development of uterine malignancy?
7. What ways, if any, may be found to avoid a repetition of these occurrences?

Detailed analyses of the two series are first presented, followed by our own conclusions and subsequent comment with respect to the experience of others.

#### 1. PATIENTS WITH CERVICAL CARCINOMA PREVIOUSLY TREATED WITH IRRADIATION FOR A SUPPOSEDLY BENIGN CONDITION

Of 481 patients with cervical carcinoma seen on the gynecologic ward service at Jefferson Medical College Hospital between 1921 and 1942, there were 7 who had received irradiation therapy for an apparently benign condition, from two to eleven years prior to the diagnosis of malignancy.

Microscopic and pathologic reports relating either to cervical or endometrial tissue or both, secured at the time of the primary treatment, were available for study, and have been reviewed in the light of subsequent developments. Brief analyses of each history, limited to pertinent facts and with appropriate comment, are appended, the patients being considered in the chronologic order in which each came to our attention. The term "menopause" is used in a restricted sense, referring merely to the cessation of uterine bleeding. Clinical grouping of the cervical carcinoma follows the Schmitz classification.

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*Sixty-Seventh Annual Meeting, June 15 to 17, 1942*  
(Concluded)

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### MALIGNANCY SUBSEQUENT TO IRRADIATION OF THE UTERUS FOR BENIGN CONDITIONS\*

LEWIS C. SCHEFFEY, M.D., PHILADELPHIA, PA.

*(From the Department of Gynecology, Jefferson Medical College Hospital)*

PUBLISHED references to the occurrence of uterine malignancy at varying intervals after irradiation for supposedly benign conditions have appeared from time to time during the past two decades. The total of reported cases is relatively small, most of them having been mentioned in follow-up studies relating to the employment of radium and x-ray for the control of benign uterine hemorrhage.

Macfarlane,<sup>8</sup> in 1932, reviewed the literature subsequent to 1915, and briefly analyzed 29 reported cases, all from German sources, adding one of her own. In addition she quoted the findings of Werner, of Vienna, and Vogt, of Tübingen, whose combined figures revealed an incidence of 0.35 per cent of uterine malignancy subsequent to the irradiation treatment of 3,980 patients for fibromyomas or climacteric bleeding. Since then mention of similar cases has appeared in articles by H. C. Taylor, Jr.,<sup>16</sup> Corseaden,<sup>2</sup> Schmitz,<sup>14</sup> Norris and Behney,<sup>9</sup> Strachan,<sup>15</sup> Luker<sup>7</sup> and Costolow.<sup>3</sup> Occasionally similar occurrences were spoken of in the appended discussions of others. All in all, 71 cases have come to our attention in this way, but we admit that other

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\*Presented at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

malignancy). Irradiation menopause six years before. History of vaginal bleeding and discharge for nearly two months prior to admission. Radium (3,600 mg. hr. and 1,500 mg. hr.) on two occasions. Death occurred one year later.

*Previous Treatment.*—On July 23, 1928, because of menorrhagia of one year's duration, a cervical polyp was removed followed by curettage and an intrauterine application of 1,200 mg. hr. of radium for small interstitial and subperitoneal myomas. A bilaterally lacerated cervix was neither biopsied nor treated. The curettings and polyp were reported to be benign.

*Comment.*—A review of the sections indicates an interval endometrium with a local hyperplasia in one area. The polyp, too, may be regarded as benign, although in one location near the surface the cells resemble epithelium, and show polynucleosis and mitotic activity, the significance of which is questionable. The most pointed criticism in the early management of this case is that cervical biopsy and treatment, either with cautery or surgery, might well have had an immediate and curative effect. It is unlikely that the presence of the previously removed polyp had any bearing on the final outcome.



Fig. 1.—Case 4 (cervical group). Area suspicious of early malignant change in cervical biopsy. (Photomicrograph  $\times 100$ .)

CASE 4.—E. D., aged 56 years, multipara, was admitted July 9, 1936. Diagnosis: squamous cell carcinoma of cervix (Group II, low grade malignancy). Irradiation menopause occurred four years previously. There was a history of bloody discharge of two weeks' duration, prior to admission. Radium therapy (3,600 mg. hr.) was given followed by subsequent external irradiation on two occasions, five months apart (1,870 r. and 1,680 r. to each of 4 ports, respectively), with survival for four years and eight months. Death was due to carcinoma.

*Previous Treatment.*—On April 21, 1932, because of menorrhagia of three months' duration and premenstrual "spotting" of one year's duration, curettage, biopsy, cauterization, and an application of 600 mg. hr. of radium to the uterine cavity for myomas were employed. In addition, a cystocele, rectocele, and an hypertrophied cervix were present. Adnexa were negative. Rapid report on the curettings and cervical tissue was requested, and this revealed an atrophic endometrium. While the biopsy sections from the cervix showed an intact

CASE 1.—S. B., aged 44 years, multipara, was admitted Jan. 24, 1933. Diagnosis: squamous cell carcinoma of cervix (Group III, low grade malignancy), with uterine myomas. No establishment of menopause. History of continuous discharge for one year; menses irregular since previous irradiation nine years before. Radium therapy (3,600 mg. hr.) followed by external irradiation (1,760 r. to each of 4 portals) was of no avail, and patient died one year later.

*Previous Treatment.*—On Nov. 12, 1924, because of metromenorrhagia and pelvic relaxation, curettage and posterior colporrhaphy were performed, together with an intrauterine application of 1,200 mg. hr. of radium for interstitial myomas. Cervix reported to be bilaterally lacerated and everted, but not biopsied or treated. Histologic report on curettage was "hyperplasia of the endometrium, suspicious of malignancy."

*Comment.*—The review of this section is informative, since it reveals a late interval endometrium, with no suggestion of malignancy. Of decidedly more interest was the discovery of a small piece of cervical tissue, evidently curetted from the portio, which shows in one location an ill-defined basement membrane with some epithelial elements infiltrating the stroma and evidencing mitotic activity and polychromatosis. Unfortunately the tissue is too minute for satisfactory diagnosis. In retrospect, criticism is tenable from several angles. First, the use of radium in a patient of 35 for the treatment of interstitial myomas, entirely apart from its failure to control adequately the growth of the neoplasm; second, the failure to biopsy and to treat properly the abnormal cervix primarily; third, the incorrect interpretation of the curettings, excusable to some extent because of the changing concepts that have evolved since then with respect to the histology of the endometrium.

CASE 2.—L. G., aged 42 years, multipara. Was admitted June 21, 1934. Diagnosis: squamous cell carcinoma of cervix (Group II, intermediate grade of malignancy) with uterine myomas. There was no establishment of the menopause. A history of menorrhagia beginning two years before was given. She was treated with external irradiation. Pronounced bleeding finally resulted in further examination, positive cervical biopsy, and application of radium therapy (4,200 mg. hr.) with subsequent external irradiation (1,600 r. to each of 4 portals). Treatment was of no avail and patient died seven months later.

*Previous Treatment.*—The patient was first seen in the Out-Patient Department on June 10, 1932, because of menorrhagia; pregnancy was excluded, and a diagnosis of myoma uteri made. Condition of cervix was not noted. Diagnostic curettage was not performed and external irradiation was instituted (1,800 r. to each of 4 portals). "Spotting" occurred subsequently at varying intervals and the patient was re-examined on five occasions during that time, but it was not until two years had elapsed that a profuse hemorrhage finally indicated cervical inspection and biopsy.

*Comment.*—Severe criticism is justifiable. First, primary inspection and careful study of the cervix were neglected; second, faulty judgment was exhibited in employing external irradiation without preliminary curettage.

CASE 3.—M. M., 49, multipara, was admitted July 29, 1934. Diagnosis: squamous cell carcinoma of cervix (Group III, intermediate grade of



CASE 7.—M. W., aged 52 years, multipara, was admitted June 13, 1941. Diagnosis: squamous cell carcinoma of the cervix (Group I, low grade malignancy). Irradiation menopause occurred six years before with intermittent bleeding during the subsequent years. There was a history of irregular vaginal bleeding of three months' duration prior to admission. On June 16, 1941, diagnostic curettage was performed. The cervix appeared to be intact; the fundus was small and freely movable. Adnexa were negative. Curettage revealed a few normal endocervical glands, presenting atrophic changes, surrounded by a poorly vascularized dense stroma, most of the tissue being replaced by islands of tumor cells of the squamous variety, well differentiated, but presenting mitotic activity and polychromatosis. It was thought that the malignant growth had its origin in the endocervix and a second curettage with cervical biopsy was requested. Five days later, on June 21, the cervical canal was dilated and thoroughly exposed for curettage of the uterine cavity and adequate biopsy. This curettage showed an interesting picture: hyperplasia of the endometrium, and side by side with it a hyalinized, degenerated, and infiltrated tissue, having no resemblance to the endometrium. There was a diffuse infiltration of tumor cells with a tendency to island and strand formation, evidencing squamous characteristics and presenting mitotic activity and polychromatosis, a well-differentiated squamous cell carcinoma of the endocervix. Biopsies from the portio showed a benign cervical erosion with hyalin changes of the cervical wall, normal squamous epithelium with an intact basement membrane. External irradiation (2,700 r. to each of four portals) was employed prior to radium therapy (4,800 mg. hr.). Patient is apparently well after one year.

*Previous Treatment.*—Because of menorrhagia and metrorrhagia of a year's duration, together with perineal relaxation, diagnostic curettage, posterior colporrhaphy, and an intrauterine application of radium (1,200 mg. hr.) for fibrosis uteri were performed on June 10, 1935. A rectocele was present, the cervix was intact, and the fundus was relatively normal in size, position, and mobility. Adnexa were negative. There was no biopsy or treatment of the cervix. Histologically, the curettings revealed only a few tiny shreds, made up of an edematous stroma in which a few fragmented glands appeared, inadequate for satisfactory diagnosis.

*Comment.*—There is little to criticize in the early management of this patient. The intact cervix did not indicate biopsy; the curettage was negative.

#### SUMMARY AND CONCLUSIONS RELATIVE TO THE CERVIX GROUP

1. All the patients were multiparas, ranging in age from 42 to 61. Radium was used to treat fibromyomas in four and x-ray in a fifth. Two were treated with radium because of fibrosis uteri, or so-called functional bleeding. A plastic, polypectomy, and vaginal myomectomy were accompanying procedures in three patients, respectively. Biopsy with cauterization was done in but one case.

2. An irradiation menopause was produced in 5 patients ranging in age from 43 to 52 years at the time of treatment. None was produced in two patients, aged 35 and 40, respectively.

basement membrane in some areas, certain others showed several islands of epithelial cells beneath it. Of these, some were well differentiated, normally appearing cells of the squamous variety; in other areas, indicating an erosion, the cells were of different sizes, showing mitosis and polynucleosis. The conclusion stated was that although the evidence was insufficient to justify a diagnosis of malignancy at the site of the erosion, nevertheless the lesion was sufficiently suspicious of early malignant change to justify a careful follow-up (Fig. 1).

*Comment.*—In this instance a golden opportunity for prophylaxis was lost, due to the indifference of the patient on the one hand and to the lack of an aggressive follow-up on the other.

CASE 5.—C. C., aged 60 years, multipara, was admitted Sept. 7, 1937. Diagnosis: squamous cell carcinoma of cervix (Group III, high grade malignancy). Irradiation menopause occurred ten years before. There was a history of vaginal bleeding for six months prior to admission. External irradiation (1,870 r. to each of 4 ports) was followed by radium therapy (3,600 mg. hr.), and a further course of external irradiation (1,300 r. to each of 4 ports, and 1,100 r. to perineum). The patient survived but one year and four months.

*Previous Treatment.*—On May 17, 1926, at the University of Pennsylvania Hospital, curettage, vaginal myomectomy and an application of 1,200 mg. hr. of radium to the uterine cavity were carried out together with hemorrhoidectomy, because of myoma uteri, pedunculated cervical myoma and hemorrhoids. There was no biopsy or treatment of cervix. Dr. Sidney Dunne reviewed the sections and established a diagnosis of normal proliferative endometrium. However, no mention was made of the condition of the cervix, and apparently there was no biopsy; neither was the cervical myoma reported histologically.

*Comment.*—It is unlikely that malignancy was present in the cervix or in the cervical myoma at the time of the first operation, for no further symptoms of consequence appeared until nearly eleven years had elapsed.

CASE 6.—C. T., aged 61 years, multipara, was admitted Aug. 29, 1938. Diagnosis: squamous cell carcinoma of the cervix (Group III, low grade malignancy). Irradiation menopause occurred nine years previously. A history of vaginal bleeding for three months before admission was given, followed by "spotting" and pain in lower right quadrant. Radium therapy (3,600 mg. hr.) followed by external irradiation (2,700 r. to each of 4 ports) was given. Patient has now survived without evidence of recurrence for nearly four years.

*Previous Treatment.*—Left oophorectomy was performed in 1903. On Jan. 24, 1929, because of menorrhagia of two years' duration, curettage, and an intrauterine application of radium (600 mg. hr.) were performed for fibrosis uteri. The cervix was reported to be lacerated, the uterus of normal size and position, and the adnexa were negative. There was no biopsy or treatment of cervix. Histologic report of the curettage reported the endometrial tissue to be hyperplastic in some areas and atrophic in others; also there was slight round cell infiltration and fibrosis of the endometrium in places.

*Comment.*—Review of the sections showed an interval type of endometrium, and no evidence of malignant change. No cervical tissue was available for study.

should include not only the portio and everted mucosa, but the lower cervical canal. The procedure ought not only to be applied to the suspected case of endometrial carcinoma but should be utilized whenever irradiation therapy is chosen for the treatment of either fibromyomas, fibrosis uteri, or functional bleeding. Eradication of any cervical pathology is equally essential.

## II. PATIENTS WITH FUNDAL CARCINOMA AND ONE WITH SARCOMA PREVIOUSLY TREATED WITH IRRADIATION FOR A SUPPOSEDLY BENIGN CONDITION

Of 124 patients with fundal carcinoma seen on both the gynecologic ward and private services during the period previously mentioned, there were 12 who had received irradiation therapy for supposedly benign lesions, from two to twenty-three years prior to the frank diagnosis of malignancy. An additional patient similarly treated ten years before subsequently developed uterine sarcoma.

Complete studies are not available in four instances, because the records of the primary treatment are either faulty or inaccessible; the remaining 9 histories are complete in all details.

### A. PATIENTS WITH INCOMPLETE RECORDS

CASE 1.—(Ward.) L. W., aged 61 years, nullipara, was admitted Dec. 11, 1924. Diagnosis: fundal carcinoma of advanced degree. Menopause occurred at the age of 51. A history of irregular vaginal bleeding of three years' duration four years after the menopause was given. At that time (1921) 1,200 mg. hr. of radium was administered at the Methodist Hospital, Philadelphia, with no report of curettage or histologic study. In 1923 the patient again received an intrauterine radium treatment for bleeding at the Lankenau Hospital, Philadelphia, at which time cancer of the uterus was said to have been diagnosed. A year later, following admission to Jefferson Hospital because of continued bleeding, curettage was performed. The vagina was atrophic, the cervix obliterated and the fundus enlarged. Sections were diagnosed as adenocarcinoma of the uterus. On Jan. 28, 1925, abdominal section revealed inoperable carcinoma of the uterus with bilateral involvement of the ovaries and metastasis to the omentum, sections of which showed adenocarcinoma, high grade malignancy. Death occurred within a few months (1925).

*Comment.*—Review of the sections of the curettage show little more than a diffuse picture of carcinoma, difficult to classify; those of the ovaries and omentum appear to be an adenocarcinoma with markedly anaplastic areas. Dr. Stanley Reimann, of the Lankenau Hospital, has also reviewed the curettage secured in 1923 and says that a diagnosis of carcinoma was not made at the time of the second radium application. In retrospect it would seem that this patient suffered from malignancy, most probably of the fundus, when she was first seen in 1921. Curettage and adequate treatment might have contributed to a more fortunate outcome.

3. The time intervening between the benign treatment and the discovery of malignancy was 2, 4, 6, 6, 9, 9, and 11 years, respectively.

4. Squamous cell carcinoma developed in every patient. Clinically, one was in Group 1, two in Group 2, and four in Group 3 (Schmitz). This is a larger proportion of relatively early cases than has been our experience with the entire series of cervical carcinoma patients. Low grade malignancy was present in 4, intermediate in 2, and high in 1. No conclusion can be drawn from this, but it can be stated that the single picture of high grade malignancy was present in the patient who developed carcinoma eleven years after initial irradiation, the longest interval noted in the series. Of 4 patients who died within one and one-half years of treatment, only 1 exhibited a low grade lesion, while of 3 other patients with low grade lesions, 1 survived for nearly five years and 2 have remained well from one to four years.

5. There is no evidence to support a statement regarding the presence or absence of malignancy at the time of the initial irradiation, with the possible exception of the one patient in whom biopsy was performed (Case 4). In this particular instance the pathologist regarded the lesion with suspicion, and even though the cervix had been cauterized, the warning should have been heeded and subsequent hysterectomy performed. With three other patients (Cases 1, 3, and 6) recorded cervical lesions should have been biopsied and treated at the time of the primary irradiation. In two additional instances (Cases 2 and 5), no note of the condition of the cervix appears, and one of these patients received x-ray therapy for fibromyomas without cervical inspection or diagnostic curettage. In the seventh patient of the series, the cervix was described as intact when first seen (Case 7).

Errors of omission may be charged to the management of 6 of these patients when they were first seen. Interest was primarily centered on the fundal lesion. Endometrial curettage was properly employed and malignancy of the fundus excluded in all instances except the one in which x-ray therapy was used. In only 2 patients, however, was the cervix thought of in terms of potential malignancy, and in one of these (Case 4) the opportunity for prophylactic treatment was missed. In the other (Case 7) biopsy of the cervical canal beyond the intact portio followed promptly when evidence of squamous cell carcinoma presented in the curettage.

6. There is no substantial evidence to show that irradiation therapy of the uterine fundus either retarded or accelerated the development of the cervical malignancy in these patients.

7. The outstanding lesson that we have learned from this phase of the investigation, and the point that we think should be emphasized to others is this: Whenever diagnostic curettage is indicated, the procedure might well be accompanied with cervical biopsy as a matter of record, but especially if any abnormality is apparent. The area of biopsy

vanced. Menopause occurred at the age of 50 years. A history of menorrhagia at intervals for two years prior to admission was given. Because of this, 2,500 mg. hr. of radium was employed in a private hospital in July, 1940. There was no regular follow-up by the physician then in charge. Bleeding never ceased entirely and in September, 1941, the patient returned to him for advice. He referred her to a radiologist who employed weekly x-ray treatments (2,300 r. anteriorly and 400 r. posteriorly to the pelvis over a period of four months). No improvement resulted, and the patient consulted me. The presumptive diagnosis was apparent. Inquiry regarding the previous treatment resulted in the negative information that the original curettage was "inconclusive" and that no sections were available for study. The general condition of the patient was poor. On Feb. 2, 1942, curettage revealed an extensive pyometra, the sections showing adenocarcinoma, intermediate grade malignancy (Grade III) with extensive necrosis and degeneration. After subsidence of fever, external irradiation was employed, solely through posterior portals (2,200 r.), because of extensive anterior abdominal wall changes resulting from the previous saturation technique. The immediate response was beneficial. On Apr. 15, 1942, curettage was repeated and intrauterine radium applied (4,575 mg. hr.). Symptomatically, the patient has improved but to date there has been little change in the pelvic findings—an enlarged uterus with moderate sensitivity. Postirradiation surgery seems unwise in this instance.

*Comment.*—Radium therapy, without effective curettage or adequate pathologic study, and without follow-up observation and subsequent treatment of value may well be responsible for the present status of the patient.

#### B. PATIENTS WITH COMPLETE RECORDS

CASE 5.—(Dr. J. M. Fisher, deceased.) M. H., aged 43 years, nullipara, was admitted May 31, 1929. Unqualified clinical diagnosis of fundal carcinoma. There was a history of menorrhagia for five months, after an amenorrhea of three years' duration (since 1926). There was no record of the pelvic findings. Complete abdominal hysterectomy with bilateral salpingo-oophorectomy was performed. Grossly there was an extensive inflammatory reaction and necrosis throughout the uterine tumor, but there was no evidence of adnexal metastases. A histologic diagnosis of adenocarcinoma, high grade malignancy (Grade IV) was made. Recovery from the operation was followed eventually by vaginal and abdominal metastases that were refractory to x-ray therapy and the patient died one and one-half years later.

*Previous Treatment.*—Through the courtesy of Dr. Sidney Dunne previous operative records and histologic reports have been reviewed by him. On Nov. 29, 1922, the late Dr. J. G. Clark performed a curettage, trachelectomy, excision of vaginal cyst, and an application of 150 mg. hr. of radium to uterine cavity because of discharge and irregular uterine bleeding. Histologically, chronic endocervicitis and typical hyperplasia of the Swiss cheese pattern was reported. Again, because of irregular bleeding, on May 31, 1923, a curettage was repeated and 400 mg. hr. of radium was administered. This time curettage still presented endometrial hyperplasia, but to a lesser degree than in the previous study. Menses were regular until 1926, when amenorrhea occurred and continued as noted until 1929, when the present illness began.

CASE 2.—(Dr. Anspach.) B. G., aged 53 years, multipara, was admitted July 21, 1927. Diagnosis: fundal carcinoma, apparently limited to the uterus. Menopause occurred at the age of 42. Recurrent episodes of bleeding for three years prior to admission, beginning eight years after the establishment of the menopause. In 1924 a curettage and an application of radium for thirty-six hours was said to have been made to the uterine cavity. No verification of where or by whom this was done had been secured, but because of this history, on Aug. 2, 1927, complete abdominal hysterectomy and bilateral salpingo-oophorectomy was performed. Enlarged lymph nodes were present in the omentum, and the uterine cavity contained an ulcerative, fungating mass that invaded the uterine wall. The adnexa were grossly normal. Histologically the tissue showed an adenocarcinoma of high grade malignancy (Grade IV). There was no demonstrable involvement of the adnexa. The patient survived the operation, but died one year later with spinal metastases.

*Comment.*—This patient very probably had carcinoma of the fundus from the onset of her postmenopausal bleeding three years before.

CASE 3.—(Dr. Anspach.) M. N., aged 52 years, nullipara, was admitted Nov. 23, 1929. Diagnosis: fundal carcinoma, apparently limited to the uterus. Menopause occurred at 40 years of age, evidently the result of radium treatment for myoma uteri, administered by the late Dr. John G. Clark at the Germantown Hospital, Philadelphia, in 1917. Six weeks prior to admission irregular vaginal bleeding had occurred, the first since the irradiation therapy twelve years before. Pelvic examination revealed an intact cervix, a mobile uterus of normal size and negative adnexa. Dr. Anspach tells me that he endeavored to secure data regarding Dr. Clark's original curettage, but a record could not be found at the Germantown Hospital; neither could Dr. Sidney Dunne find any record in the gynecologic laboratory at the University of Pennsylvania. On Nov. 26, 1929, curettage was performed and 2,400 mg. hr. of radium applied to the uterine cavity. Histologic report was adenocarcinoma of high grade malignancy (Grade IV). Sections were also submitted to Dr. C. C. Norris, who was reluctant to make a frank diagnosis of malignancy, but advised treating the lesion as carcinoma. On Jan. 21, 1930, complete abdominal hysterectomy and right salpingo-oophorectomy were performed. The left adnexa was densely adherent and was not removed. Multiple small myomas were present in the uterus, the endometrial cavity of which was entirely necrotic. Beneath this rather shallow area there was rather extensive infiltration of the musculature by masses of epithelium which in some places involved the entire thickness of the uterine wall. This tissue was undifferentiated and formed small solid masses. The removed right tube was uninvolved, the right ovary harboring a simple cyst. Postoperative courses of x-ray therapy were employed, but pelvic recurrence and pulmonary metastasis resulted in the death of the patient three years later.

*Comment.*—It is unfortunate that nothing definite can be stated with regard to the initial curettage by Dr. Clark, but from our knowledge of his meticulous procedures, it may be assumed that there was no question of malignancy twelve years prior to its discovery by Dr. Anspach.

CASE 4.—(Dr. Scheffey.) L. M., aged 65 years, multipara, was admitted Jan. 31, 1942. Diagnosis: fundal carcinoma, fairly well ad-

were diagnosed but not treated. Bleeding ceased for a year and then recurred slightly every five or six months over a period of four years until January, 1932, when curettage and radium therapy were employed. This caused cessation of bleeding for seven years when readmission was necessitated by the appearance of a pinkish discharge. Cervix was intact, and the fundus somewhat enlarged and irregular but freely movable. Adnexa were negative. On Dec. 17, 1938, curettage was performed and radium placed in the uterine cavity pending a rapid report on the curettings. This revealed an adenopapillary growth of low grade malignancy (Grade I), and a dosage of 4800 mg. hr. was employed. There have been no return of symptoms to date.

*Previous Treatment.*—At the time of the primary curettage and radium treatment (2,400 mg. hr.) on Jan. 8, 1932, the curettings were reported as revealing small areas of hyperplastic columnar epithelium with irregular acini in the superficial layers of the myometrium, the cells being hyperchromatic, varying in size and shape, with many of the small acini lined by numerous layers of epithelium instead of one. The diagnosis was summed up as follows: "The change in the epithelium of the endometrium is very suggestive of malignancy, but serial sections were cut from the tissue and many sections examined from various levels of the tissue, and no frank evidence of definite infiltration by the epithelium could be demonstrated."

*Comment.*—A review of the original sections lead us to believe that the lesion should have been regarded as a definite low grade malignancy (Grade I) from the first. Radical operation should have followed the irradiation therapy in due time. Surgery was contraindicated in 1938.

CASE 8.—(Ward.) B. S., aged 60 years, nullipara, was admitted Apr. 18, 1939. Presumptive diagnosis: fundal carcinoma. There was a history of vaginal bleeding of five months' duration, the first time after an irradiation menopause produced thirteen years before (1926). Cervix was intact, fundus normal in size and position, and adnexa negative. Curettage was performed on Apr. 22, 1939, and radium was placed in the uterine cavity pending a rapid report of the curettage. This was diagnosed adenocarcinoma, low grade malignancy (Grade II) (Fig. 3). A total dosage of 4,800 mg. hr. of radium was employed. There have been no further symptoms. On May 22, 1941, the cervix was dilated and the uterine cavity sounded. No bleeding was produced, but no curettage was performed. Patient was apparently well three years later.

*Previous Treatment.*—On Sept. 27, 1926, because of menorrhagia and metrorrhagia, curettage was followed by radium (1200 mg. hr.) which was employed to control functional bleeding. Pelvic examination was grossly negative. Sections from the curettings were reported as "poly-poid endometritis" and no further treatment was advised (Fig. 2).

*Comment.*—Review of the original section in this case leads us to believe that the original diagnosis was a mistaken one. It is similar to the recent one, and should be regarded as an adenocarcinoma of low grade malignancy (Grade II). The astonishing feature of this case is the subsidence of clinical symptoms for a period of thirteen years after a relatively small irradiation dosage. In view of this fact, and because of the patient's advanced age (60), together with a certain degree of asthenia, it was thought advisable to depend upon the larger dosage of radium, and post-irradiation surgery was not advocated.

*Comment.*—In this instance a preceding hyperplasia was present. Review of the sections showed a mixed growth to be present: in one location there was small acini formation, though not very well differentiated. Side by side with this area were rather well-defined islands and strands of tumor cells of squamous variety. It is possible therefore that the sections represent both fundus and endocervix, or it might be regarded as an adenoacanthoma.

CASE 6.—(Ward.) R. R. 57, nullipara, was admitted Dec. 29, 1936. Diagnosis: pelvic tumor. History of an irradiation menopause existing for ten years, and discomfort in the lower left pelvis for three weeks. There was some vaginal discharge but no bleeding. Pelvic examination revealed a cystocele, rectocele, and cystic cervix; the fundus was irregularly enlarged to the size of an eight weeks' pregnancy, and there was also an enlargement in the right adnexal region that suggested a parovarian cyst. General condition was inferior. Because of the uterine enlargement, which suggested a myoma, and after an adequate period of observation, on Jan. 23, 1937, diagnostic curettage was performed and radium placed in the uterine cavity, pending a rapid report of the curettage. This proved to be malignant and a dosage of 3,000 mg. hr. was employed. The cervix was not biopsied, since it presented no eversion, and was not friable. Histologically the sections were reported as revealing a highly degenerated tissue, devoid of glandular elements, in the less degenerated portions of which the connective tissue stroma showed diffuse infiltration by epithelial cells, unequal in size and irregular in shape. Some areas presented small clumps of epithelial cells, but a diagnosis of high grade malignancy, solid adenocarcinoma of the fundus (Grade IV), seemed warranted. The therapy was ineffectual and the patient died in three months' time.

*Previous Treatment.*—Ten years before (1927), curettage followed by radium therapy (900 mg. hr.) had been performed at Hahnemann Hospital, Philadelphia, because of excessive vaginal bleeding. A marked fibrosis of the lower fundus and upper cervical canal was observed clinically together with a cervical erosion. No biopsy was done. Curettage was insufficient for diagnosis, but the patient remained under observation for two years (1929), and there was no further bleeding. For this information I am indebted to Dr. N. V. Ludwick, radiologist at Hahnemann Hospital. On Nov. 9, 1935, appendectomy was performed by Dr. K. E. Fry, on the general surgical service at Jefferson Hospital. Pathologically, acute suppurative appendicitis was reported. No pelvic examination was recorded on the occasion of this admission, and there was no note in the operative report of any pelvic pathology being observed at the time of the appendectomy.

*Comment.*—Principal interest in this case attaches to the peculiar character of the curettage. No errors of omission can be attributed to the clinical management. There seems to be no relationship between the primary treatment for fibrosis uteri and later developments. A pelvic examination at the time of the operation for acute appendicitis might have been revealing.

CASE 7.—(Dr. Scheffey.) B. C., aged 61 years, multipara, was admitted Dec. 16, 1938. Presumptive diagnosis: fundal carcinoma. Menopause occurred at 42 years of age (1919), followed soon afterward by vaginal bleeding, becoming excessive at 50 (1927), when myoma uteri



hysterectomy and bilateral salpingo-oophorectomy were performed. An interstitial myoma was observed in the anterior uterine wall. There was no gross evidence of extension or metastasis from the uterus. The mucosa was thickened in several areas of the uterine cavity, being friable and partially invasive of the myometrium at these places. The adnexa appeared atrophic. Sections revealed an adenocarcinoma of low grade malignancy, as did the previous diagnostic curettage. No metastatic lesions were observed in the tubes and ovaries. Convalescence was complicated by three distinct attacks of pulmonary emboli, but recovery was complete. There is no evidence of recurrence to date.

*Previous Treatment.*—During a period of eighteen months prior to admission, patient had been receiving external irradiation for the treatment of fibromyomas by a radiologist; this in view of the fact that the bleeding was definitely postmenopausal; neither had diagnostic curettage ever been performed.

*Comment.*—Further comment would be superfluous.



Fig. 4.—Case 10 (fundal group). Mucocellular adenocarcinoma, intermediate grade of malignancy (adenocarcinoma, Grade III). (Photomicrograph  $\times 50$ .)

CASE 10.—(Ward.) E. H., aged 55 years, multipara, was admitted Jan. 15, 1941. Presumptive diagnosis: fundal carcinoma. There was a history of bloody vaginal discharge of six months' duration, the first since the initiation of an irradiation menopause with radium eleven years before (1930). Cervix was intact, slightly enlarged symmetrical fundus, and adnexa were negative. Curettage on Jan. 16, 1941, revealed an unusual histologic picture, viz., "arborescent tumor growths consisting of many incomplete acini and papillary formations, composed of large cells containing large nuclei surrounded by a great deal of cytoplasm, and resembling mucin cells." Diagnosis, mucocellular adenocarcinoma fundus uteri, and intermediate grade malignancy (Grade III) (Fig. 4). The curette distinguished a submucous tumor, and complete hysterectomy was deemed advisable after necessary attention to patient's general condition, since on a previous admission cerebrospinal syphilis had been diagnosed, although serology was now negative. On Feb. 12, 1941, complete abdominal hysterectomy and bilateral salpingo-oophorectomy was performed. Grossly, fibromyomas were present in the uterus in addition to the carcinomatous growth invading the myo-

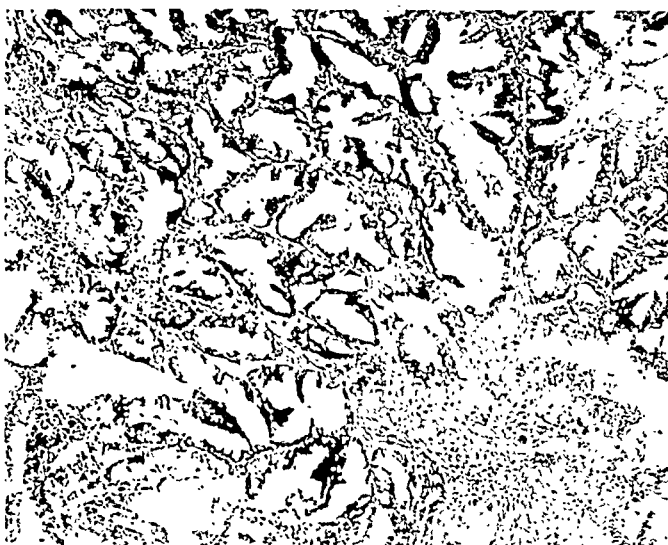


Fig. 2.—Case 8 (fundal group). Low grade malignancy (adenoma malignum, Grade II), reported thirteen years before as "polypoid endometritis." (Photomicrograph  $\times 50$ .)

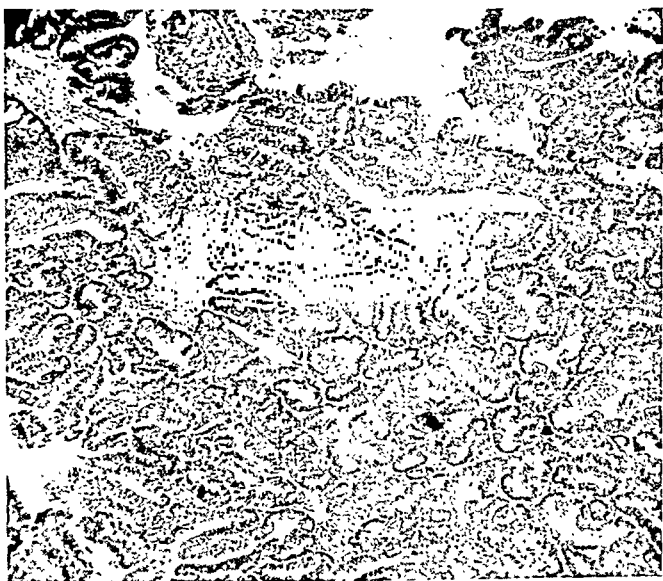


Fig. 3.—Case 8 (fundal group). Low grade malignancy (adenoma malignum, Grade II), when carcinoma was finally diagnosed. (Photomicrograph  $\times 50$ .)

CASE 9.—(Dr. Scheffey.) M. S., aged 60 years, multipara, was admitted Mar. 26, 1940. Presumptive diagnosis: relatively advanced fundal carcinoma. Menopause occurred at 35 years of age. There was a history of intermittent vaginal bleeding of two years' duration, but of daily occurrence for three months prior to admission. Cervix was intact, slightly enlarged symmetrical uterus, and adnexa negative with exception of bilateral tenderness on deep palpation. On Apr. 1, 1940, curettage was done and radium placed in the uterine cavity pending a rapid report of the curettage. This revealed an adenocarcinoma of low grade malignancy (Grade II). Radium dosage of 5,400 mg. hr. was employed, and six weeks later, on May 16, 1940, complete abdominal

CASE 12.—(Dr. Anspach.) R. H., aged 44 years, nullipara, was admitted March 10, 1941, because of an attack of lower abdominal pain, accompanied with an enlargement of the uterus and left adnexa. Presumptive diagnosis: fundal carcinoma with accompanying chronic pelvic inflammatory disease. There was a prolonged history of antecedent vaginal bleeding with numerous curettements which will be described in detail. On March 13, 1941, complete abdominal hysterectomy, bilateral salpingectomy, and right oophorectomy were performed (the appendix and possibly the left ovary had been removed many years before). Stenosis was present at the site of the internal os, and the endometrial cavity was the site of an adenocarcinoma of low grade malignancy (Grade II) that deeply penetrated the myometrium (Fig. 6). A left hematosalpinx was present, the ovary being absent; the right adnexa were lightly adherent, but otherwise normal. There was no histologic evidence of metastases. Postoperative external irradiation followed, and the patient is apparently well a year later.

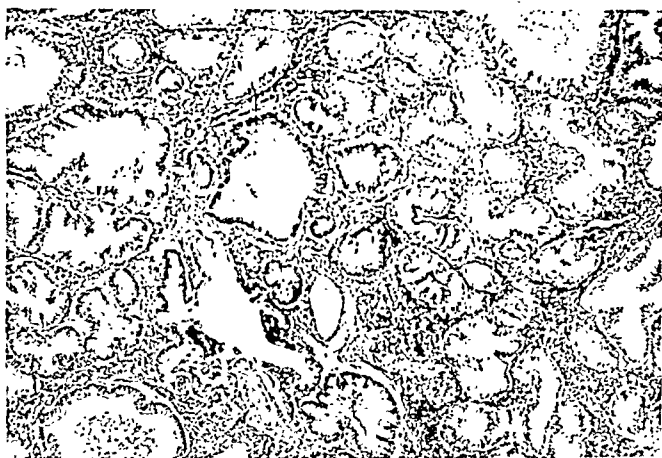


Fig. 5.—Case 12 (fundal group). So-called "carcinoid hyperplasia" discovered in 1933. (Photomicrograph  $\times 50$ .)

*Previous Treatment.*—The earlier course of this patient and the treatment accorded is lengthy but unusually interesting. In September, 1918, at the age of 21, Dr. John G. Clark performed a curettage for irregular uterine bleeding. This helped for two months. In December, 1918, Dr. Clark again performed a curettage together with abdominal hysterotomy because of a possible uterine myoma; a cystic left ovary was either removed or punctured, and an appendectomy was done. A year later (1919), because of recurrent bleeding, curettage followed by 350 mg. hr. of radium, was employed. This treatment was repeated two years later (1921) when there was further recurrence. Dr. Sidney Dunne has been unable to find any record of sections from these various curettages, but evidently nothing of a malignant nature was suspected or found; very probably, in view of the history, the condition was one of typical hyperplasia as we know it today. For eleven years the patient remained well and had married. In 1932 (aged 35), menstruation again became irregular and Dr. Anspach performed a curettage on Nov. 11, 1932, the curettings showing a marked premenstrual function. A year later, for continued irregularity curettage was again resorted to, with a radium application (300 mg. hr.) on Nov. 14, 1933. There was a relatively slight enlargement of the uterus. Drs.

metrium. The adnexa were grossly normal. Histologically the sections were similar in appearance to those secured at the time of the diagnostic curettage. Recovery from operation was uneventful and patient has remained well to date.

*Previous Treatment.*—In 1918, when patient was 32 years of age, a pelvic tumor was said to have been removed in the Chester, Pa., Hospital. This was not verified. On July 28, 1930, when patient was 44, polypectomy with curettage and an intrauterine application of radium (1,200 mg. hr.) were performed because of metromenorrhagia of two months' duration, supposedly due to the polyp and to uterine myomas. Surgery was discouraged at that time because the patient had positive serology (blood and spinal fluid), and cerebrospinal syphilis was thought to be present. Histologically the sections from the curettage revealed atrophic endometrial glands and marked fibrosis of the stroma with beginning calcific formation. The cervical polyp presented an erosion, both cylindric and squamous epithelium, but was benign.

*Comment.*—No relationship seems probable between the histologic studies made at an interval period of eleven years. Of interest is the unusual picture of mucocellular adenocarcinoma.

CASE 11.—(Dr. J. B. Montgomery.) S. W., aged 49 years, multipara, was admitted Feb. 15, 1941. Presumptive diagnosis: fundal carcinoma, relatively early. There was a history of vaginal bleeding of one month's duration, the first to appear following an irradiation menopause of four years' duration. Cervix was intact, retroflexioversion of uterus with small myoma in fundus, and adnexa were negative. Because of the recurrent bleeding and suggestive history of malignancy, complete abdominal hysterectomy and bilateral salpingo-oophorectomy were performed on Feb. 19, 1941. Grossly there was no extension or metastasis from the uterus, the myometrium of which was deeply infiltrated by an adenocarcinoma of intermediate grade malignancy (Grade III). Uneventful recovery. Patient has remained well to date.

*Previous Treatment.*—Because of menorrhagia of seven weeks' duration thought to be due to fibromyomas in a patient aged 45, curettage and cervical biopsy were performed, and intrauterine radium (600 mg. hr.) was employed on Nov. 2, 1937. Sections from the biopsy revealed a benign erosion of the cervix. Those from the curettage presented a rather bizarre picture, nearly the entire stroma being replaced by numerous glandular formations with hardly any interglandular stroma in some places. The glands, unequal in size and dilatation, and lined by several layers of cells with centrally situated nuclei, could scarcely be called malignant. The lesion was termed "carcinoid hyperplasia" and Dr. Hoffman, who coined the phrase, warned that the patient be kept under close observation and that subsequent curettings be examined from time to time. This was done. Consequently recurrence of bleeding four years later was promptly observed and treated as noted.

*Comment.*—The admonition of the pathologist, combined with accurate clinical observation, resulted in radical treatment. The other point of interest is the designation of the original lesion as "carcinoid hyperplasia," which might be regarded by some as the equivalent of the term "papillary adenoma malignum" but which in our opinion is an atypical endometrial hyperplasia so marked as to histologically mimic the latter.

bleeding and colicky pelvic pain of six weeks' duration. Menopause occurred at the age of 42, with a subsequent history of bloody vaginal discharge beginning at 61, and appearing sporadically over an interval of six months (1931) when therapy effected a cessation of the symptoms. The present complaint was promptly managed by Dr. F. L. Nugent, who performed a curettage and applied radium (2,000 mg. hr.) at the Reading Hospital in April, 1941. (This had been preceded two years before by estrogenic therapy for six weeks.) The sections were reported as uterine sarcoma of high grade malignancy by the pathologist, Dr. E. D. Funk, and the patient was referred for an opinion as to future therapy in view of the author's previous knowledge of the patient (Fig. 7). Examination revealed an indurated, irregular but intact cervix, and a probe produced bleeding from the cervicouterine

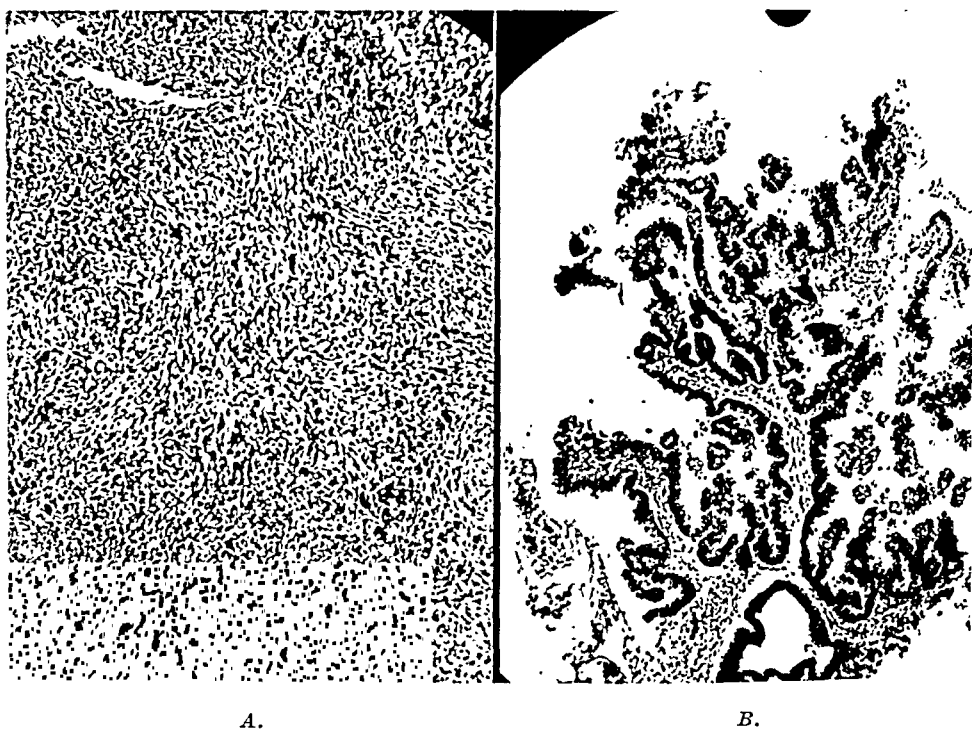


Fig. 7.—Case 13 (fundal group). A, Myosarcoma of uterus. B, Area in same section, suggestive of adenocarcinoma or hyperplasia. (Photomicrographs  $\times 100$ .)

canal. The fundus was enlarged and somewhat fixed, with a sensitive nodulation in the cul-de-sac. Adnexa were not distinguishable. We were in complete agreement with the diagnosis made from the section submitted, and further irradiation therapy was advised. The patient died within three months, and autopsy revealed diffuse sarcomatosis of the abdomen, verifying the previous diagnosis of myosarcoma of the uterus.

*Previous Treatment.*—Diagnostic curettage followed by radium (1,200 mg. hr.), with removal of a cervical polyp, and cervical biopsy had been performed by the author on May 12, 1931, because of intermittent bloody vaginal discharge occurring twenty years after the establishment of the menopause. At that time, in addition to a cystocele and rectocele of moderate degree, the cervix showed old lacerations with slight eversion and polyp formation. The fundus was of normal size

B. L. Crawford and Jacob Hoffman both felt that the lesion was most probably an adenocarcinoma of low grade malignancy (Grade II), although the diagnosis of "carcinoid hyperplasia" was tenable (Fig. 5). Sections were submitted to Dr. Charles Norris and to Dr. Joseph McFarland. The opinion of the former was that the lesion was benign but that in view of many extremely atypical features and because of the repeated bleeding, operation was advisable. Dr. McFarland's advice was essentially the same. Nevertheless, the husband, a physician, refused surgical treatment, and the patient was left alone. The symptoms then remained in abeyance for several years, but recurred in 1935, and on Dec. 12, 1935, Dr. Anspach again did a curettage and applied radium (300 mg. hr.). This curettage was similar in most respects to that reported in 1933, although it was conceded that the glands approached a more normal appearance. In view of the gratifying response to the previous irradiation, surgery was again refrained from. Curiously enough, the uterus became smaller, and the patient remained



Fig. 6.—Case 12 (fundal group). Low grade malignancy (adenoma malignum, Grade II), revealed at operation in 1941. (Photomicrograph  $\times 50$ .)

symptom free for six years, when at the age of 44, without external bleeding, pelvic pain and the discovery of a pelvic mass made operation imperative, and this decision was now concurred in by the husband, with findings as noted.

*Comment.*—Much could be said about this case. Granting an earlier condition of endometrial hyperplasia, it would seem that much trouble could have been avoided if the advice relative to operation in 1933 had been accepted, for the lesion was then regarded as very likely malignant on exceptionally strong grounds. It is astonishing to realize that relatively small radium dosage evidently retarded the growth of this possibly low grade carcinoma over a period of eight years. Another feature to be emphasized is that the stenosis of the cervical canal, evidently acquired during this period, seemingly prevented external bleeding for some time, so that an hematosalpinx resulted from the unreleased blood associated with the developing carcinoma, which finally caused sufficiently painful symptoms to warrant investigation and discovery of a pelvic mass.

CASE 13.—(Dr. Scheffey and Dr. Nugent.) A. B., aged 71 years, multipara, was seen in consultation on May 1, 1941, because of vaginal

tients with low grade malignancy, from one to four years. These findings are in accord with our experience in the complete fundal carcinoma series.

5. Carcinoma was perhaps present in 6 patients at the time of the initial irradiation therapy. This assumption is very probably true in Cases 1, 2, and 4, where radium was applied with questionable curettage, since no record of the latter could be found and adenocarcinoma was definitely proved to be present within three years thereafter. Carcinoma was evidently present in Case 9 when x-ray therapy was administered for fibromyomas without diagnostic curettage and a low grade lesion was found within two years. In Cases 7 and 8, review of the original sections indicated lesions of low grade malignancy, the actual diagnosis being made six and thirteen years later, respectively, when irregular bleeding recurred. In these instances errors in judgment were evident.

In four patients in whom malignancy was discovered from 10 to 12 years later (Cases 3, 6, 10, 13), no errors of omission seem to have played a part, and the neoplastic process might be regarded as a late independent one.

Special interest attaches to the remaining 3 patients: In Case 5 radium therapy was twice used at the age of 36 to control proved hyperplasia, and seven years later a high grade adenocarcinoma was discovered, treated by hysterectomy, with death occurring a year and a half later with metastases.

In Case 11, "carcinoid hyperplasia" was diagnosed at 45 when radium was applied for a fibromyoma. Return of symptoms in four years was promptly treated with radical surgery and an intermediate grade of lesion was found. Patient living and well for more than a year.

In Case 12, implied hyperplasia was repeatedly treated with radium beginning at the age of 21. At 35 "carcinoid hyperplasia" or what some might call a low grade malignancy, was discovered and again irradiated; finally at 44 indisputable carcinoma was found at radical operation after the return of symptoms. This patient has remained well for over a year.

No criticism can be leveled at the management of Cases 5 and 11. Surgery would long before have been resorted to in Case 12 but for the repeated objections of the husband to radical operation.

6. In only two instances, Cases 7 and 8, have we factual evidence to indicate that radium may have retarded a malignant growth, for review of the curettings secured 6 and 13 years before when the radium was used to control supposedly benign bleeding, showed definitely malignant lesions. With recurrence of symptoms and repetition of curettage and radium therapy, adenocarcinoma of low grade malignancy was found present with an advance in abnormal morphologic structure. Even so it is admittedly an assumption to regard these malignant growths as quiescent over these years, for the appearance of a newer neoplastic process cannot be readily disproved. Attempting to draw

and position and the adnexa were negative. The curettage showed hyperplasia of the senile endometrium and fibrosis of the stroma. The cervical tissue and polyp revealed nothing to suggest malignant change.

*Comment.*—Review of the earlier sections in comparison with the recent ones designated myosarcoma gave no indication of any relationship.

#### SUMMARY AND CONCLUSIONS RELATIVE TO THE FUNDAL GROUP

1. Nine of the patients were multiparas, 4 were nulliparas; the ages ranged from 43 to 71. Four patients were treated for fibromyomas (Cases 3, 9, 10, 11), 3 with radium and 1 with x-ray. Five were treated with radium, supposedly for postmenopausal functional bleeding (Cases 1, 2, 4, 7, 13), but in the first three of these the earlier records are incomplete. Two were treated for fibrosis uteri or functional bleeding (Cases 6, 8), and 2 for typical hyperplasia (Cases 5 and 12). Trachelectomy, hysterotomy, and cervical biopsy were accompanying procedures in 3 patients, respectively (Cases 5, 8, 10), and polypectomy with biopsy was performed in 2 patients (Cases 10, 13). Curettage accompanied the radium applications in all except the patient treated with x-ray, but no record of the examination of the curettings could be found in 4 of them (Cases 1, 2, 3 and 4).

2. An irradiation menopause was produced in 5 patients, ranging in age from 40 to 47 at the time of the initial treatment. None occurred in 2 patients aged 22 and 36, respectively. In 6 patients, from 50 to 61 years of age, the bleeding was postmenopausal, occurring from four to twenty years after its establishment. In no instance did the natural menopause occur after 50 years.

3. The time intervening between the benign treatment and the diagnosis of malignancy was 2, 2, 3, 3, 4, 6, 7, 10, 10, 11, 12, 13, and 23 years, respectively.

4. Myosarcoma occurred in one patient in the fundal malignancy group. Adenocarcinoma was eventually diagnosed in 12 patients, being early or only moderately advanced clinically in all but 3 of them. This proportion does not vary appreciably from the clinical extent of the lesions noted in our total series of fundal malignancies. In this particular group of patients, there were 4 with low grade, 3 with intermediate, and 5 with high grade malignancy. One intermediate grade lesion was unusual, a mucocellular adenocarcinoma.

There is no demonstrable relationship between the time interval following the initial irradiation therapy and the grade of malignancy that finally occurred; neither is there any between the age when the malignancy developed and its gradation.

As regards the final outcome, however, it is interesting to note that no patient with high grade malignancy survived treatment for more than three months to a year, and the same applies to the patient with myosarcoma. The 3 patients with an intermediate grade of malignancy have remained well from four months to a year and one-half; the 4 pa-



no sections were available for review. This case, added to those of two patients treated with radium, in one of whom preceding hyperplasia was a proved finding, and implied on good authority in another, makes a total of three instances of pre-existing typical hyperplasia in our complete series of 124 patients with fundal carcinoma. No statement can be made with respect to coexisting hyperplasia and adenocarcinoma, because sections of all the fundal malignancies observed have not been reviewed. The cystic hyperplasia found previously in the one instance of myosarcoma that occurred was typical of the senile endometrial pattern recently reported by Novak and Richardson, Jr.

Of serious concern to us has been the lesion that has been referred to as "carcinoid hyperplasia," a term that we have employed to describe atypical endometrial hyperplasia which is so marked as to resemble histologically the low grade lesion generally referred to as papillary adenoma malignum (Grade I), although there is no definite distinguishing feature that would label it as carcinoma. It might be regarded by some as an extreme grade of hyperplasia; by others as a very low type of malignancy. The stroma cells show mitotic activity. The glandular structures are greatly increased in number and, as in true hyperplasia, show a marked disparity in size. At times they may present bizarre convolutions. They are lined by several rows of cells which show mitotic activity. Proliferation of the cells may be so marked as to result in polypoid formations which extend into the lumina of the glands. A distinguishing feature is the sparsity of the stromal elements, as a result of which the glands lie very close to each other and almost fuse. Two such instances have been described (Cases 11 and 12) in which adenocarcinoma definitely developed later on. This experience has taught us to regard such lesions as essentially malignant and to manage them accordingly.

A decade ago Howard Taylor, Jr., stated in the summary of an exceptional survey of the subject that "whether from a practical standpoint, hyperplasia is to be regarded as precancerous and treated as such, must remain an open question." That the question still is an open one, is evident from the divergent views to which expressions have been, and continue to be given.

Eardley Holland, in discussing the paper of Norris and Behney on "Radium Irradiation for Benign Hemorrhage" in 1936 stressed the importance of learning whether or not radium in the uterus has any effect in increasing the incidence of fundal carcinoma. He felt that there was no such connection but believed that the possibility ought to be "definitely settled one way or the other." Similar and some opposing views have been expressed by others. With respect to the group developing cervical carcinoma, there was no evidence that irradiation per se had either retarded or accelerated its development. As regards the fundal carcinoma group, the only statement of fact that can be

any conclusions relative to the primary effect of the earlier irradiation in retarding the development of malignancy in the other patients (excluding those in whom the condition was probably present at the outset, Cases 1, 2, 4, and 9), is equally fallacious, as is speculation relative to the initiation or acceleration of malignancy by irradiation in this series of patients. A statement of fact that can be made is this: The response to irradiation with radium has been more effective in the low grade and intermediate grade lesions than in those of the high grade variety, as evidenced by the surviving patients exhibiting the low and intermediate grades of malignancy.

7. The analysis of the fundal group emphasizes certain truths that are almost self-evident. Irradiation therapy should always be preceded by or accompanied with diagnostic curettage, and all curetted material, no matter how inconspicuous, should be thoroughly examined and carefully interpreted. Fibromyomas should never be regarded as the sole cause of postmenopausal bleeding until an accompanying adenocarcinoma of the endometrium has been ruled out. So-called functional or climacteric bleeding should be viewed with similar suspicion. Among 12 patients with adenocarcinoma pre-existing typical hyperplasia was reported twice, with definite proof in one instance; polyps were found twice, both being benign. Of special interest was the lesion that we have termed "carcinoid hyperplasia" present in one and possibly two patients in the series. The single patient with myosarcoma (Case 13) exhibited a prior senile type of hyperplasia and a benign cervical polyp.

#### DISCUSSION

This presentation has been centered upon a survey of the relationship between irradiation for supposedly benign conditions and the subsequent development of uterine malignancy. The role of cervical lesions, which some term "precancerous," has been appropriately mentioned with respect to the group of patients in whom carcinoma of the cervix developed, and certain conclusions have been stated. The controversial question pertaining to the association between endometrial hyperplasia and adenocarcinoma of the fundus has not been entered into in detail; its occurrence in a few of the earlier curettements has merely been stated as a fact.

In this respect, and apart from the irradiation phase of the problem, it is of interest to note that in the complete series of patients with fundal carcinoma, three records of previous curettements without irradiation therapy are available, and they may be recalled to advantage. In two of these women, treated for abnormal bleeding, an interval endometrium was present two and six years before, the former developing a high grade, and the latter a low grade malignancy at 50 and 45 years of age, respectively. The third patient, developing a low grade lesion at 68, had been curetted twelve years previously by Dr. G. M. Laws, who informed us that "glandular hyperplasia" had been found, but that

## DISCUSSION

DR. CURTIS F. BURNAM, BALTIMORE, MD.—The necessity of a thorough preliminary examination cannot be emphasized enough, when using intrauterine radium. This applies to many other kinds of treatment, especially where bleeding or tumor is concerned. Certainly, a routine examination under anesthesia and a curettage should precede every hysterectomy, and especially supravaginal hysterectomies. Dr. Howard W. Jones, of our Clinic, has recently reviewed a series of 754 consecutive primary cancers of the cervix. Fifty-one of these, almost 7 per cent, were of the cervical stump. Sixteen, of the 51, developed within less than two years of the operation, slightly more than 2 per cent.

Our observations indicate that anaplastic carcinomas of the uterine body are much more radiosensitive than histologic low grade cancers. The outlook for clinical cures and survivals is, however, inversely proportional to the grade of malignancy, provided the disease is still limited to the uterus. Where the disease is beyond the uterus, a clinical cure is more likely with an anaplastic growth. Average survival is likely, however, to be longer in the low grade cancers.

The microscopic descriptions given by Dr. Scheffey are very interesting, but need little comment. The term "carcinoid" or "canceroid" in this connection is new to me, but the microscopic picture is an old and familiar one. Such conditions may persist unchanged for years. Often, if thoroughly curetted before a hysterectomy, no evidence of trouble is demonstrable in the removed organ.

We have done very little radiation for postmenopausal bleeding of benign origin, but have no evidence that it is harmful, or that it may not control bleeding. One must remember that even curettage may not disclose an existent cancer. Two cases illustrate this: (1) the first was a physician's wife who had had a curettage on two occasions with very small amounts of normal tissue obtained, after a further six months of bleeding she consulted another physician, who found a now enlarged uterus and abundant cancerous material. (2) The second case was that of a maiden lady with senile vaginitis, low ionizable blood calcium, and a small uterus. On account of bleeding she was curetted but no tissue could be obtained. For two months she was put on estrogen therapy and an appropriate regime to correct the calcium deficiency. The vaginitis cleared markedly, calcium levels reached normal, but bleeding continued. The uterus was still small, but abundant cancerous material was now obtained on a second curettage.

The question may be asked as to whether intrauterine radiation increases the probability of corpus, other gynecologic cancers, or cancer generally? One would think so, especially of cancer of the body of the uterus, rectum, and bladder. Having observed several endometrial cancers in our series about ten years ago, we have turned to x-ray for the treatment of benign bleeding. It has proved equally effective, more accurately controlled, and much more plastic in adjustment to each individual case.

Naturally, a starting point would be a knowledge of the frequency of cancer of the corpus. Very interesting vital statistics are available as to the occurrence of uterine cancers, but there is no accurate division between those originating in the cervix and body by any of the authorities I have consulted.

I have just analyzed 625 cases, treated with intrauterine radium, between January, 1912, and January, 1920. In this group, we have full records for more than ten years, and in nearly all for much longer periods. You will observe that in 625 cases there developed 25 malignancies, or a little less than 4 per cent. Their distribution was as shown in Table I.

Having no other source of information, I have attempted to estimate the relative percentages of cervix and body cancers as they have occurred in our clinic: In 5,173 cases, taking all ages, the cervix cases constituted a little more than 87 per cent, the corpus cases over 12 per cent, and sarcomas less than 0.9 per cent. Taking only patients aged from 55 up the ratio between body and cervix cancers is ap-

made from this study is that malignant lesions of low or intermediate grade responded more favorably to irradiation than did those of high grade character. With respect to this observation, Healy, Burnam and others have repeatedly stressed the value of irradiation therapy either alone or preliminary to surgery in the treatment of fundal carcinoma. There was also reason to assume that in two cases at least, unrecognized lesions of low grade malignancy may have been held in abeyance for a considerable time. With regard to the lesions that were primarily benign, such a supposition is purely speculative. Norris has called attention to his experience in sectioning postradiated uteri, declaring that in most instances he was "unable to see anything under the microscope that indicated previous irradiation, other than senile changes which were general throughout the endometrium."

From the analyses of these two series of patients, it is our conclusion that errors of omission, either in technique or in judgment as commented upon, and not the irradiation therapy itself, were the responsible factors in the subsequent occurrence of malignancy in the particular instances mentioned; in the absence of such errors, the retarding influence of the irradiation is more or less speculative.

The lessons learned and the steps suggested to diminish the possibilities of similar developments have been outlined in the respective summaries and need not be repeated.

In the compilation and preparation of this work, I am not only indebted to my former chief, Dr. B. M. Anspach and to my immediate associates for their cooperation in supplying information, but to colleagues in other institutions who have similarly aided me, and these acknowledgments are mentioned throughout the text. Much of the pathologic material in years gone by was reported by the late Dr. Baxter L. Crawford, former pathologist to the Jefferson Hospital. More recently these studies have been made under the direction of Dr. C. J. Bucher, present pathologist to the Hospital with the active cooperation of Dr. Jacob Hoffman, departmental pathologist, who has helped considerably with the histologic interpretations.

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The radiation dosage used in the benign lesions of the corpus in general was much less than would now be regarded as adequate for the conditions treated. This is, however, understandable as some of these cases were treated at a time when our knowledge of radiation effects was not well defined.

Regarding his cases of corpus carcinoma, I would like to comment upon Case 12 with a pathologic report on the curettings of "carcinoid hyperplasia." Such a report is unsatisfactory to a surgeon and suggests an uncertain frame of mind on the part of the pathologist. That uncertainty should have been enough to require the gynecologist to increase the radium dosage or remove the uterus. The pathologist cannot in every case give us an exact histologic diagnosis, but he can report doubt or suspicion on borderline cytologic changes or pictures. The responsibility for the proper treatment of the case rests with the gynecologist.

Incidentally, may I say that nowadays it is well recognized that intrauterine dosages of radium below 1,000 mg. hr. or moderate dosages of x-ray may retard growth activity in so-called low grade endometrial cancers such as adenoma malignum grades 1 or 2 for several years, during all of which time the patient may be symptom free. This explains why Dr. Scheffey found that some of his patients, even some years after their radiation treatment, were still fair risks for operation.

The patients with the higher histologic types of cancer, of course, were unfortunate and failed to survive later treatment by radiation or surgery as the original radiation dosage was far too inadequate for that histologic grade of cancer.

Finally, I think as specialists in diseases of women we should be meticulous to a fault in the treatment of benign cervical lesions and benign uterine bleeding with or without fibromyomata in women of any age. If radiation methods have been used to treat the benign lesion, I would advise against discharging such a patient from observation two or three years later because she is symptom free and the pelvic organs appear to be normal. I think it would be much better to encourage such patients to report once a year for a check-up.

DR. CHARLES A. BEHNEY, PHILADELPHIA, PA.—In administering radiologic treatment for benign hemorrhage the gynecologist assumes the responsibility of ruling out carcinoma. The importance of routine histologic examination of ample specimens from diseased cervixes is convincingly demonstrated in Dr. Scheffey's presentation. Even when biopsy is practiced, the sample is often inadequate and diagnostic curettage should be more than a few scrapings from the lower uterine segment. The chance of a small growth evading the curette or the biopsy scalpel can never be entirely eliminated, but if this possibility is always remembered, the potential error can be reduced. A satisfactory biopsy from the cervix should consist of a wedge which includes a portion of the cervical canal, the diseased area and some adjacent healthy tissue. In order to determine the exact origin of a malignant tumor of the uterus, we have found it useful to secure three separate specimens for microscopic study. The first consists of curettings from the cervical canal to the internal os; the second from the uterine cavity above the internal os; and the third, a generous specimen from the cervix. In this way there is less danger of mistaking an adenocarcinoma originating in the cervical canal for fundal malignancy. One should endeavor to explore every part of the uterine cavity with the curette, paying particular attention to the top of the endometrial cavity and the cornua. Dr. George Gray Ward has devised special curettes better to reach the more inaccessible parts of the uterine cavity.

Dr. Scheffey's case of low grade carcinoma, proved to be of at least thirteen years' duration, again demonstrates that the life cycle of carcinoma may be much longer than was generally supposed.

In 1936, Dr. Charles Norris and I reported the results of radium irradiation for benign uterine bleeding to this Society. Our series, from the gynecologic service of the University Hospital, comprised 687 cases of myomas of the uterus, and 750 cases of myopathic hemorrhage, a total of 1,437 patients. Of these, 1,006

TABLE I

|                                   | NUMBER OF<br>CASES | PERCENTAGE | TIME OF DEVELOP-<br>MENT                              |
|-----------------------------------|--------------------|------------|---|
| Cancers of the body of the uterus | 5                  | 0.8        | 1- 6 yr. 2-12 yr.<br>1-14 yr. 1-17 yr.                |
| Sarcoma of the body of the uterus | 1                  | 0.16       | 12 yr.  |
| Cancer of the cervix              | 3                  | 0.5        | 2- 4 yr. 1- 8 yr.                                     |
| Cancer of the vulva               | 3                  | 0.5        | 1-10 yr. 1-16 yr.<br>1-21 yr.                         |
| Cancer of the ovary               | 1                  | 0.16       | 7 yrs.  |
| Cancer of the breast              | 7                  | 1.12       | 1- 5 yr. 2- 8 yr.<br>1-18 yr.<br>1-14 yr.<br>1-20 yr. |
| Other cancers                     | 4                  | 0.64       |   |
|                                   | 1 Small bowel      |            | 4 yr.   |
|                                   | 1 Large bowel      |            | 9 yr.   |
|                                   | 1 Tongue           |            | 7 yr.   |
|                                   | 1 Liver            |            | 23 yr.  |

proximately as 1 to 2. From the sources we draw our material, practically all cervix cases are referred to us, but a good many corpus cancers are not. I would venture to guess that from the age of 55 and over, corpus cancers are at least as common as cervical cancers.

It is of interest that only 1 out of 6 of my cases of corpus malignancy developed in less than 12 years of the original radiation treatment, whereas Dr. Scheffey had 10 out of 13.

I believe the ordinary use of intrauterine radium for benign conditions does not cause an increase in body, cervical, or other cancers. The total cancer mortality closely approximated, taking age into consideration, is that found in the papers on vital statistics.

DR. WILLIAM P. HEALY, NEW YORK, N. Y.—Dr. Scheffey's paper presents an interesting topic for our consideration and at the same time he asks an important question. Is there an etiologic relationship between the application of radium in the treatment of benign uterine lesions and the occasional subsequent development of a malignant lesion such as cancer in the same organ?

I agree fully with his conclusion that in his reported cases there is no evidence to support such an opinion. This question has been raised from time to time heretofore by others, not only with regard to the therapeutic use of radium but also regarding x-ray therapy.

The unusually large opportunity which I have had in the past twenty-one years to observe the effects of radiation therapy as utilized in the treatment of human tumors, has presented me with many instances of the occurrence of multiple primary tumors in the same individual and frequently in the same organ. Often these tumors have been coincidental, at other times one type of growth has preceded the other by an interval of time varying from months to many years.

Probably the most common combination of tumor types have been uterine fibroids and benign breast lesions. Following these, I would place uterine fibroids and carcinoma of the corpus, and next in order uterine fibroids and carcinoma of the breast. Carcinoma of the cervix in spite of its great frequency is seldom associated with other histologic types of tumor, which is interesting since uterine fibroids are so common that one would expect a frequent association of the two tumor types.

It is evident that uterine fibroids represent the common denominator and the other types of tumor are the variables. I have a feeling that in human beings, as in animals, we have tumor-bearing individuals or strains, families if you will. How common it is for a gynecologist to operate upon each of several sisters in a family for fibromyomas.

# THE FUNCTIONAL ANATOMY OF LABOR, WITH SPECIAL REFERENCE TO THE HUMAN BEING\*

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THE primate uterus is a highly differentiated structure and, from the viewpoint of functional anatomy, presents six more or less distinct problems: (1) the cause of the onset of labor;<sup>1-4</sup> (2) the mechanism of polarity;<sup>4-6</sup> (3) the mechanism of the coordination of the fused longitudinal halves; (4) the mechanism of "retraction";<sup>7</sup> (5) the mechanism of the dilation of the cervix;<sup>8-12</sup> and (6) the mechanism of the separation of the placenta.<sup>13, 14</sup>

The objectives of this paper are: (1) to correlate the course of the wave of contraction with the morphologic pattern of the uterine musculature in the human being; (2) to summarize the evidence regarding the growth of the isthmus uteri and its unfolding and inclusion as a part of the general uterine cavity during pregnancy in the human being and monkey; and (3) to report certain observations resulting from measurements made on all the frozen sections of the human uterus reported in the literature.

## I. THE WAVE OF CONTRACTION AND THE ARCHITECTURE OF THE UTERINE MUSCULATURE

*The Wave of Contraction.*—In 1930, Ivy, Hartman and Koff<sup>10</sup> directly observed the contracting primate uterus of the rhesus monkey in labor. The typical wave of contraction consists of two waves which start bilaterally and synchronously from an area located in the region of the insertion of the Fallopian tubes. The areas (the "pace-makers") are located about 1.5 cm. ventral and cranial to the insertion of the tubes. The areas appear to be constantly quiescent in that they do not blanch during uterine contraction. The wave on each side spreads as a widening wave, elliptical in form. As the wave from each longitudinal half of the uterus approaches the midline the corpus is observed to shorten longitudinally and a circular contraction appears at the level of the insertion of the round ligaments. This circular wave of contraction moves caudalward over the lower segment and finally involves the cervical sphincter. The spread of the wave of contraction is diagramed in Fig. 1.

It was quite evident that the musculature in the region of the placental site is less involved in the contraction than the remainder of the uterus. Occasionally a wave of contraction was observed to be initiated only on one side, producing a bulging of the opposite side or an obliquity

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were followed up for two or more years, and 300 (184 myoma uteri and 521 functional hemorrhage cases) for from ten to twenty years after treatment. In this series, uterine carcinoma was discovered subsequently eight times, an incidence of about 0.8 per cent. Carcinoma was also found once in each of the following situations, the ovary, the bladder and the rectum.

Radiologic treatment of uterine bleeding, presumed to be of benign origin, should be practiced only after careful investigation of the cervix and fundus, and patients so treated should be followed up at regular intervals for the rest of their lives. When symptoms recur, hysterectomy rather than re-irradiation is the procedure of choice.

DR. ISIDOR C. RUBIN, NEW YORK, N. Y.—Two points may be made with regard to prophylaxis against neglected or undiscovered carcinoma of the uterus. First, diagnostic curettage in the presence of a carcinoma of the uterus may cause it to spread into deeper parts. Second, diagnostic curettage often fails to reveal intrauterine lesions, including submucous fibroids, polyps, and carcinomas. For these reasons I have felt it necessary to resort to x-ray visualization of the endometrial cavity, using a viscous, soluble, crystalloid iodine solution in cases of postmenopausal bleeding when one suspects a polypoid condition or carcinoma. This substance needs to be introduced only in the small amounts of 1.5 to 2.0 c.c. In our service we have turned to this substance because of the bad reactions obtained from lipiodol. In several instances we have in this way revealed the presence of submucous polyps or cornual carcinoma which was missed on a previous curettage.

DR. JOHN A. MCGLINN, PHILADELPHIA, PA.—We have heard about the many cases which have been treated with radium without thorough investigation. This Society should also take cognizance of the present practice of treating benign bleeding with hormones. A woman who is bleeding from the uterus deserves the most careful investigation and no one is justified in using radium, still less a substance given by hypodermic injection, without previous careful examination. We will often miss carcinoma which might have been recognized early simply on account of the modern treatment of hemorrhage by hormones.

DR. SCHEFFEY (closing).—Dr. Healy and Dr. Burnham have a right to object to the term "carcinoid hyperplasia." It is not my intention to attempt to introduce a new term into the literature, but merely to describe a controversial lesion. The designation "carcinoid hyperplasia" was suggested by our departmental pathologist, Dr. Hoffman, and is used to describe those curettings about which there is so much doubt regarding proper classification. Some may consider such a lesion as definitely malignant, calling it "papillary adenoma malignum"; others may regard it as extreme hyperplasia, as was the case in this particular instance. What we have learned practically from this experience is that when we do encounter a lesion such as this we shall not hesitate to regard it primarily as malignant and treat it accordingly.

The systematic follow-up of all patients who have had irradiation for benign conditions has been properly emphasized by all of the discussors, and I know that our experience has made us more conscious than ever of the importance of continued attention to patients following such therapy.

Dr. Behney has approached the problem somewhat differently, showing the subsequent occurrence of one cervical and of seven fundal carcinomas in 1,006 patients treated with irradiation for benign conditions. I agree with him entirely in the careful technique that he has outlined for securing adequate tissue from all sources of the uterus by thorough curettage and biopsy.

Dr. McGlinn brought up the question of indiscriminate hormonal therapy and I agree with him heartily in his denunciation of it. In our experience we have seen too frequently the loss of valuable time because injections of hormones have been used thoughtlessly to control abnormal menopausal and postmenopausal bleeding without adequate examinations.



Goerttler made thick sections of fresh fetal, mature, pregnant, and nonpregnant human uteri. The sections were dehydrated by a special process and carefully stretched to separate slightly the fibers. The sections were then dusted with graphite or gold bronze dust. The excess was removed and the sections were examined in intense light. This permitted a detailed study of the course of the muscle fasciculi.

His observations, which are most pertinent to the present discussion, follow. The myometrium is composed essentially of two interlacing, spiral systems of muscle fasciculi. The origins of these two systems are traced to the unfused Müllerian ducts. The diagrams of the disposition of the two muscular systems are shown in Fig. 2. They have a striking

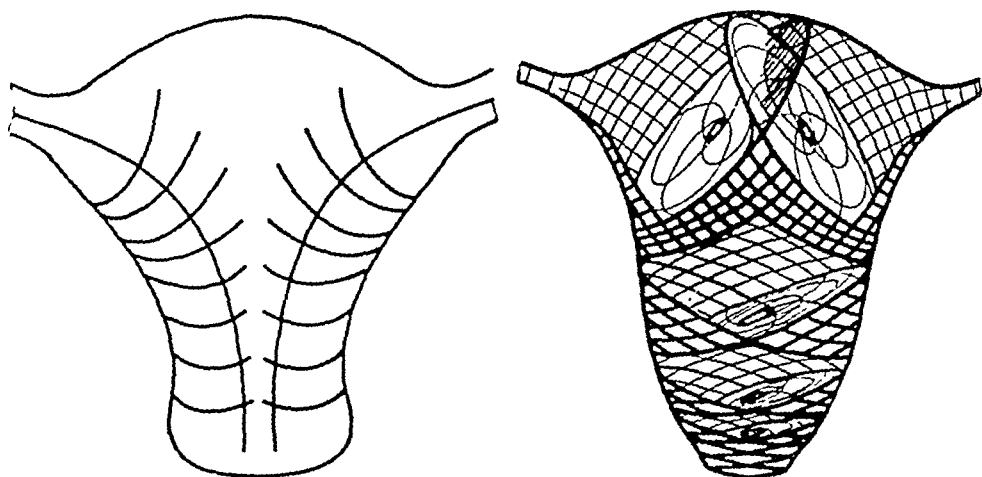


Fig. 2.—Diagrams, redrawn from Goerttler, illustrating his findings on the arrangement of the two chief systems of muscular fasciculi in the nonpregnant uterus, which result from the fusion of the Müllerian ducts. The diagrams should be compared with the route of travel of the contraction wave, as illustrated in Fig. 1.

similarity with our description of the mode of travel of the wave of contraction in the monkey's uterus. Some of the older anatomic descriptions of the uterine musculature, also show the orbicular arrangement of muscle fasciculi about the insertion of the tubes.

*Comment.*—Thus, a structural as well as a comparative anatomic and physiologic background appears to exist for the described mode of travel of the wave of uterine contraction in the primate uterus.

## II. THE GROWTH AND UNFOLDING OF THE ISTHMUS UTERI IN PREGNANCY

In briefly reviewing and summarizing the evidence regarding the growth and unfolding of the isthmus uteri in pregnancy, one is interested in answering three questions: (1) Does the isthmus uteri grow and unfold to become a part of the uterine cavity in pregnancy? (2) Does it form only a part of the lower uterine segment? or (3) Does it form the entire lower uterine segment during pregnancy? How much the true histologic cervix contributes to the lower segment in labor is a separate question.

### A. THE MONKEY

When Rudolph and I<sup>c</sup> described the mechanism of parturition in the bicornuate uterus of the dog, it was suggested that the fused portion

of the uterus. Such an atypical wave of contraction sometimes passed to the opposite side and again died out at the midline.

Hofbauer<sup>15</sup> has described a somewhat similar wave of contraction in the human uterus, which he observed during a cesarean section under spinal anesthesia and after the intramuscular injection of pituitrin. His description differs from ours chiefly in regard to the site of origin of the wave of contraction which he placed in the midline rather than in the region of the insertion of the tubes.

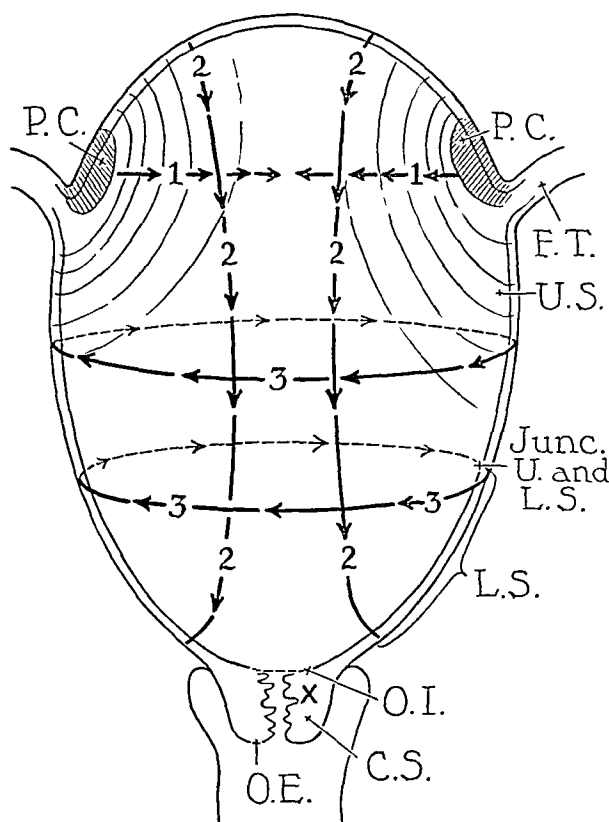


Fig. 1.—A diagram illustrating the passage of the wave of contraction over the primate uterus of the rhesus monkey. "1" represents the waves that spread from the area (P.C., pacemaker) slightly above and ventral to the insertion of the tubes; "2," the longitudinal shortening that occurs as the orbicular, "1," waves reach the midline; "3," the circular peristaltoid wave that is seen to start near the insertion of the round ligaments and travels downward to involve the cervical sphincter located in the region of the obstetrical internal os (I.O.).

*The Architecture of the Human Uterine Musculature.*—When we originally described the wave of contraction, a complete study regarding the architecture of the primate uterine musculature was not available. Therefore, Ivy, Hartman, and Koff<sup>10</sup> could not satisfactorily correlate the structure of the myometrium with the mode of travel of the wave of contraction. It was pointed out, however, that the mode of origin and travel of the contraction wave correlated with the mode of travel that one might anticipate from a consideration of comparative anatomy and physiology.<sup>5-7, 16</sup>

In the meantime, Goerttler<sup>17</sup> has published a complete study of the architecture of the human myometrium. The results of his study, though they require confirmation, correlate well with our description of the mode of travel of the wave of contraction.

that of the isthmus, and that of the isthmus is different from that of the corpus. A glance at Fig. 3 shows that the difference may be recognized grossly in a thin sagittal section.

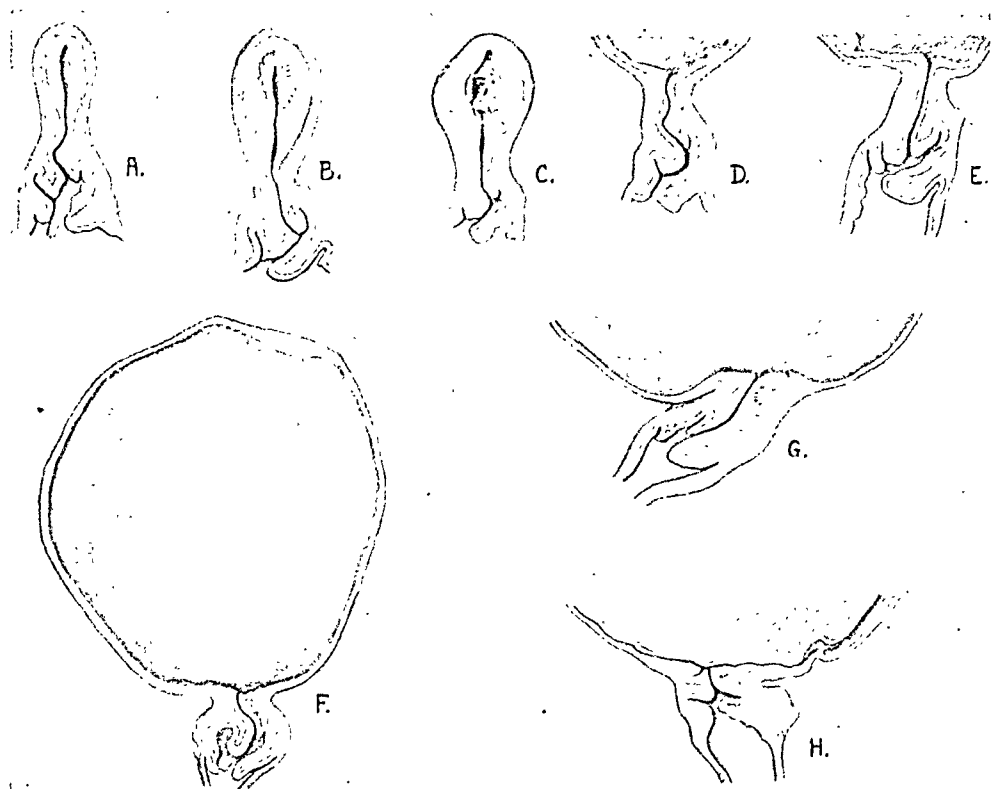


Fig. 4.—A copy of Franke's<sup>10</sup> specimens showing the growth and then the unfolding of the isthmus into the general uterine cavity in pregnancy. *A*, 16-celled ovum is present in tube; length of uterus is 3.6 cm.; A-P diameter is increased. Note internal and external lips of cervix, isthmus, and hyperplasia of mucosa of corpus. *B*, anterior and posterior placentas are visible; length of uterus is 4.6 cm.; A-P diameter is 1.7 cm. There is no decidual reaction in isthmus; mucosa of cavity is greatly thickened. Note internal and external lips of cervix. *C*, embryo and 2 placentas are visible; length of uterus is 3.8 cm., A-P diameter is 1.9 cm. In this specimen the decidual reaction extends into upper portion of isthmus. External and internal lips are evident, though anterior and exterior lip is small. *D*, fetal parts have been removed; length of uterus is 6.5 cm.; A-P diameter is 3.3 cm. The isthmus is longer than normal. The interior and exterior cervical lips are evident. *E*, fetal parts have been removed; length of uterus is 7.1 cm.; A-P diameter is 4.0 cm. The isthmus is still quite long. *F*, fetal parts have been removed; length of uterus is 8.45 cm.; A-P diameter is 6.3 cm. The isthmus has obviously unfolded. Note the interior and exterior lips of the cervix. *G*, fetal parts have been removed; length of uterus is 11.6 cm.; A-P diameter is 8.0 cm. The external cervical lips still hang like tongues downward; the internal cervical lips are now more horizontal, the isthmus having unfolded. *H*, fetal parts have been removed; length of uterus is 11.3 cm.; A-P diameter is 8.5 cm. Both cervical lips now lie horizontally. It is more typical for the internal lip to lie horizontally and the external lips to hang downward, as will be noted in the frozen sections of Danforth, Graham and Ivy.<sup>18</sup> In *F*, *G*, and *H* the internal lips of the cervix form the obstetric internal os.

*The Obstetric Internal Os Is Grossly Labeled in the Monkey.*—The crucial proof that the isthmus grows and becomes included in the general uterine cavity in the monkey rests chiefly on the fact that Nature has grossly labeled the obstetric internal os, or the junction of the true histological cervix with the histological isthmus. The macaca uterus has two cervical lips, an internal and an external (Fig. 3). The external lip forms the external os. The internal lip marks the site of the obstetric internal os in the nonpregnant, pregnant and laboring organ<sup>18</sup> (see Fig. 4).

of the canine uterus was homologous with the isthmus uteri of the human uterus. The evidence for the homology was derived solely from a consideration of the embryology and the comparative anatomy and physiology of the uterus. A similar induction was made by Ivy, Hartman and Koff<sup>10</sup> when they described parturition in the rhesus monkey.

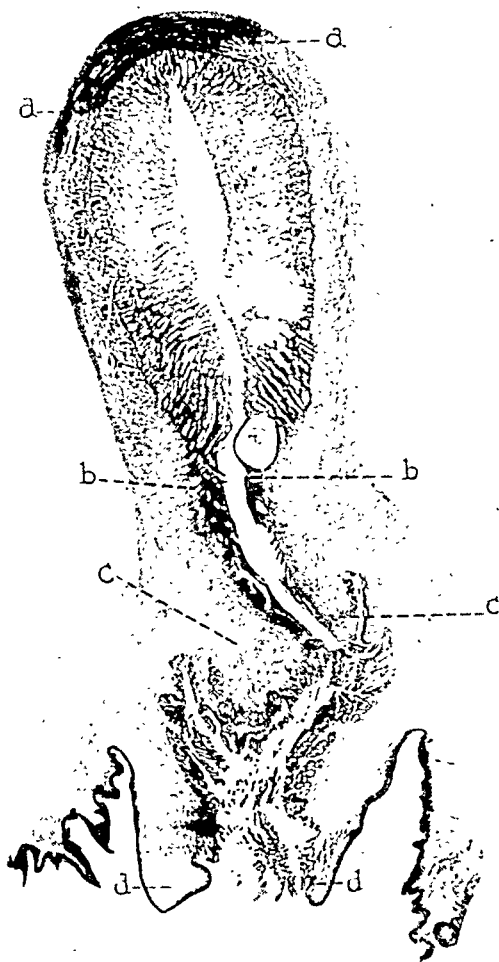


Fig. 3.—Sagittal section of the nongravid uterus of the rhesus monkey. "b" indicates the junction of the corpus with the isthmus [orificium isthmi internum (Stieve), or os internum anatomicum (Aschoff)]. "c" indicates the junction of the isthmus with the true histological cervix [orificium isthmi externum or orificium canalis cervicis internum (Stieve), or os internum histologicum (Aschoff)]. "d" indicates the external os [orificium canalis cervicis externum, or orificium uteri externum (Stieve)]. A small cyst, which is rather common in the human isthmus (ref. 20), is seen at the level of the internal orifice of the isthmus. True cervical glands are evident up to "c." Between "c" and "b" typical isthmic mucosa occurs. It is to be emphasized that the internal cervical lips, designated "c" constantly mark the obstetrical internal os during the latter part of pregnancy and labor in the monkey.

Anatomic evidence is now available which proves that in the primate uterus of the monkey the isthmus uteri grows and unfolds to become a part of the general uterine cavity during pregnancy. This evidence will be briefly presented.

*The Parts of the Monkey Uterus (Macaca rhesus and Macaca cynomolga).*—The uterus of *Macaca* is very definitely divided into three parts.<sup>18, 19</sup> The specialized epithelium of the true cervix is different from

the monkey. (B) The site of the obstetric internal os or the upper limit of the true histologic cervix is not grossly labeled in the human being, though it is histologically labeled until the second stage of labor is approached. (C) In the process of full-term labor much of the true cervix mucosa is stripped off.<sup>18, 19</sup>

*The Isthmus of the Nonpregnant Human Uterus.*—The histology of the human isthmus has been described by numerous investigators.<sup>11, 12, 20-25</sup> The mucosa of the isthmus is much like that of the corpus, except that it is much thinner and the glands are more sparse. It manifests relatively little menstrual and decidual reaction.

The length of the human isthmus is apparently subject to considerable variation in the nongravid state. Aschoff gives a length of from 7 to 10 mm.; Stieve, of 4.5 mm.; Frankl, 5 to 9 mm.; Sabotta, 5 mm.; Oertel, 8 mm.; and Acosta-Sison, 7 to 10. According to our estimates the isthmus of the monkey (*Macaca*) makes up about 20 per cent and that of the human being (average 7.3 mm.) about 10 per cent of the total length of the nonpregnant uterus.

*The Growth and Unfolding of the Isthmus in Pregnancy.*—Stieve,<sup>11, 12</sup> who has made the most extensive study, finds that the isthmus increases in length two to three times before it unfolds to be included in the general uterine cavity. I have summarized and tabulated the data he presents. It is presented in Table I. The data show that during the first four to ten weeks of pregnancy the isthmus elongates two to three times, depending on the average length taken for the isthmus in the non-gravid state.

#### A. Histologic Studies.

1. *The Mucosa:* In view of Stieve's studies, and those of others,<sup>22, 25</sup> on the mucosa in the region of the obstetrical internal os, the isthmus unfolds and is included in the general uterine cavity between 10 and 12 weeks of pregnancy. Then, the upper limit of the true histologic cervix is at the level of the obstetrical internal os (Table I). *This, I believe, constitutes the strongest type of evidence in support of the unfolding of the isthmus in pregnancy in the human being.*

2. *The Musculature:* Goerttler,<sup>17</sup> in his histologic studies of the muscular fasciculi of the human uterus, made studies on the gravid and non-gravid human uterus. He reports that in the nongravid uterus the "circular" muscular of the isthmus lies almost horizontal (Fig. 2). In the gravid uterus as pregnancy advances the muscular fasciculi assume a steeper course. In the cervix, however, the circular or horizontal architecture of the fasciculi persists through pregnancy. In the corpus, the architecture is not significantly modified in the pregnancy. This evidence indicates that the growth and unfolding of the isthmus in pregnancy results in a modification of its architecture. It supports the evidence derived from a study of the mucosa of the obstetric cervix at different stages of pregnancy.

3. *The Membranes:* The relatively loose attachment of the membranes to the lower uterine segment has been used in support of the view that the isthmus forms the lower segment. Stieve,<sup>12b</sup> who believes that the isthmus forms the entire lower segment prior to labor, makes the following points: (a) the membranes are loosely attached to the lower segment; (b) the muscular wall of the lower segment is thinner through-

*The Isthmus Uteri of the Nongravid Monkey.*—The mucosa of the mesial aspect of the external lip contains typical mucous secreting cervical glands. This is true also of the inferior and inferior mesial aspects of the internal lip. The mucosa of the cranial mesial portion of the internal lip, where the mucosa of the isthmus begins, does not contain mucus-secreting cells or glands (Fig. 3, and ref. 19). The mucosa of the isthmus extends upward for a distance of 6 to 10 mm., according to our observations, where it joins the definitely thicker mucosa of the corpus. The point of transition is histologically quite definite.

*The Isthmus Uteri of the Monkey in Pregnancy.*—According to Franke,<sup>19</sup> the mucosa of the isthmus of the monkey manifests only a slight decidual reaction. An inspection of Fig. 4 shows that early in pregnancy the isthmus retains its general form. As pregnancy advances it grows in length and becomes included into the general uterine cavity so that the internal lip, lying in a horizontal plane, forms the obstetric internal os. This was confirmed<sup>18</sup> in our frozen sections of the monkey prior to the onset of labor.

Since the pregnancies of Franke's specimens were not dated, the time of initiation and completion of the unfolding of the isthmus cannot be stated. However, the isthmus has almost completely unfolded when the total length of the uterus has increased 2.6 times.

#### CALCULATION

1. Average length of non-gravid uterus (ref. 18) 3.2 cm.
2. Average length of gravid uterus at almost complete unfolding<sup>19</sup> 8.45 cm.
3. Calculation:  $8.45 \div 3.2 = 2.6$  times increase in length.

*Comment.*—The evidence showing that the isthmus uteri unfolds and is included in the general uterine cavity of the uterus of the monkey is clear-cut and decisive. Thus, the isthmus uteri in the monkey either contributes to the formation of the so-called lower uterine segment, or actually is the lower uterine segment.

Whether the isthmus forms the entire lower uterine segment, exclusive of the cervix, is not known. We hope to settle this question by placing some nonabsorbable material in the musculature at the level of the physiologic retraction ring and locating its site in the involuted uterus.

*The Extent to Which the Cervical Lips Contribute to the Lower Uterine Segment in Labor.*—The internal cervical lip in the monkey, when it is effaced and dilated in labor, contributes a small but variable part to the lower uterine segment. The external lip is generally retracted beneath and external to the internal lip. Sometimes, however, the internal lip is markedly separated from the external lip, so that a wall of 1.0 to 1.5 cm. intervenes between the base of the internal and external lip. This is particularly true posteriorly (see Figs. 8 and 9, ref. 18).

#### THE HUMAN

The evidence for the growth, unfolding and inclusion of the isthmus uteri into the general uterine cavity in pregnancy in the human being is perhaps not as clear-cut and decisive as in the monkey. The reasons for this apparently are: (A) The isthmus of the nongravid human uterus, as identified histologically, is relatively less extensive than in

out pregnancy (this may be questioned by frozen section evidence) and labor than that of the corpus; (c) the true cervix does not enlarge in pregnancy as does the isthmus and corpus; (d) the mucosa of the lower segment in late pregnancy is thin, there are no decidual cells and the epithelial cells are flat and the spongiosa is thinner; (e) the amnion and chorion are thinner over the lower segment and are tough due to connective tissue. These points are generally recognized as being true. However, it is difficult, if not impossible, after the isthmus has unfolded, to identify a clear-cut line of demarcation between the upper and lower segments. The evidence regarding the membranes is only suggestive. It is only corollary in my opinion to the other more conclusive histologic evidence, showing that, as pregnancy advances, the isthmus unfolds.

*B. Gross Anatomic Evidence of the Unfolding and Growth of the Isthmus in Pregnancy.* If the isthmus of the human being grows and unfolds and continues to grow to form the lower uterine segment, there should be some gross anatomical evidence of these changes.

1. *Hegar's Sign:* As early as 1893, Dickinson,<sup>27</sup> in describing the early signs of pregnancy, referred to Hegar's sign as being due to the compressibility of the isthmus or lower uterine segment. About four to seven weeks after the last menstruation, on bimanual examination, the compressible isthmus is found between the hard cervix and the elastic body of the corpus. This sign may, however, be due to the softening and increase in the diameters of the cervix. The sign is only corollary evidence in that it might be expected to occur at six weeks when the isthmus has grown appreciably (Table I).

2. *Changes in Form and Growth of the Uterus During Pregnancy.*—It was thought that if the isthmus grew in length and then unfolded some significant change in the form of the uterus might occur. To examine this possibility, frozen sections made during the early months of pregnancy were measured and Stieve's data were analyzed.

First, as indicated above, we know when the isthmus unfolds in the monkey, because the junction between the true cervix and isthmus is grossly as well as histologically labeled. It has almost completely unfolded when the length of the gravid uterus has increased 2.6 times over the nongravid length.

In the human being, using Stieve's data, the isthmus was unfolded when the length of the uterus had increased approximately 2 times ( $14.0 \div 7.3 = 1.9$  times). Inspection of the frozen sections (Table II), without microscopic evidence, indicates that the isthmus appears to be unfolded completely in the four-month sections when the uterus has increased in length, 2.2 times ( $16.3 \div 7.3 = 2.2$  times); whereas, in the five-month sections when the uterus has increased in length 2.9 times ( $21.0 \div 7.3 = 2.9$ ), the isthmus appears to be unfolded. This evidence is only of interest in that it checks well with the more definite evidence on the monkey.

Second, after the initiation of pregnancy the length of the uterus increases continuously to term (Tables I and II, and Fig. 5). The uterus also increases in breadth and thickness (anteroposterior diameter) during the first four weeks (Table I and Fig. 6). But, according to the data in Table I, the uterus does not definitely increase in breadth and thickness during the period of from four to eleven weeks; then, a definite increase in breadth and thickness occurs (Table I and Fig. 6). It would appear that something occurs at eleven or twelve weeks which rather suddenly results in an increase in breadth and thickness of the

TABLE I. ANALYSIS OF STIEVE'S CASES (34), ABNORMAL AND INCOMPLETE CASES BEING OMITTED

| LENGTH OF<br>FETUS MM. | CASES | WEEK<br>OF<br>PREG. | UTERUS       |               |               | CX.<br>+<br>IS.<br>MM. | CX.<br>MM. | IS.<br>MM. | VERT. EXT.<br>LENG. OF<br>CAVITY<br>MM. | CONDITION OF<br>ISTHMUS   |
|------------------------|-------|---------------------|--------------|---------------|---------------|------------------------|------------|------------|---|---------------------------|
|                        |       |                     | LENG.<br>MM. | BREAD.<br>MM. | THICK.<br>MM. |                        |            |            |   |                           |
| Nonpregnant            |       | Nulli               | 68           | 49            | 27            | 32                     | 27         | 5          | 36                                      |                           |
| Nonpregnant            |       | Multi               | 78           | 55            | 31            | 34                     | 27         | 7          | 44                                      |                           |
| 2.8-10.8               | 4     | 4-5                 | 93           | 81            | 75            | 36                     | 26         | 10         | 57                                      | Isthmus not un-<br>folded |
| 14.5-27.0              | 6     | 6-8                 | 104          | 80            | 67            | 42                     | 29         | 13         | 62                                      | Isthmus not un-<br>folded |
| 39.5-52.5              | 6     | 9-10                | 124          | 83            | 72            | 43                     | 28         | 15*        | 81                                      | Isthmus not un-<br>folded |
| 64.0                   | 1     | 11                  | 133          | 82            | 75            | --                     | 35         | --         | 98                                      | Isthmus unfolded          |
| 82.0-92.0              | 4     | 13                  | 142          | 105           | 95            | --                     | 33         | --         | 109                                     | Isthmus unfolded          |
| 96.0                   | 1     | 14                  | 152          | 114           | 107           | --                     | 36         | --         | 116                                     | Isthmus unfolded          |
| 108.0                  | 1     | 15                  | 161          | 116           | 111           | --                     | 34         | --         | 127                                     | Isthmus unfolded          |
| 114.0-119.0            | 3     | 16                  | 166          | 120           | 106           | --                     | 37         | --         | 129                                     | Isthmus unfolded          |
| 146.0                  | 1     | 20                  | 206          | 135           | 124           | --                     | 38         | --         | 168                                     | Isthmus unfolded          |
| 151.3-157.0            | 2     | 21                  | 200          | 139           | 127           | --                     | 36         | --         | 164                                     | Isthmus unfolded          |
| 165.0-172.0            | 3     | 22                  | 194          | 133           | 111           | --                     | 30         | --         | 164                                     | Isthmus unfolded          |
| 182.0-188.0            | 2     | 23                  | 221          | 156           | 139           | --                     | 28         | --         | 193                                     | Isthmus unfolded          |

Isthmus of the nonpregnant uterus varies from 4.5 to 10 mm. in length: Aschoff (0.5-0.9); Frankl (0.7-1.0); Oertel (0.8); Sabotta (0.5); Acosta-Sison (0.7-1.0); Stieve (0.45).

\*Longest isthmus Stieve found in pregnancy before unfolding was 22 mm. Note that during four to eleven weeks no change in breadth or thickness of uterus occurred on the average, but there is an increase in length. After isthmus unfolds, there is an increase in breadth and thickness. (Stieve, H.: *Ztschr. f. Mikr.-anat. Forsch.* 11: 291, 1927; 14: 549, 1928.)



3. Increase in sagittal circumference between 4th and 6th months = 26.9 cm.
4. Calculated Increase:
  - a. Expected increase based on growth in previous 3 mo. =  $2 \times 6 = 12$  cm.
  - b. Contributed by unfolding of isthmus: 14.6 cm.
  - c. Total increase = 26.6 cm.

The calculated and experimental figures check remarkably well.

This evidence does not prove that the isthmus actually unfolds in the manner described, because we have no way of knowing what changes would occur if the isthmus did not unfold. The sudden spurt in growth rate might be due to growth stimuli (hormones and distention). However, the evidence is certainly suggestive that unfolding has occurred, particularly when considered together with the more conclusive evidence for a similar process in the monkey.

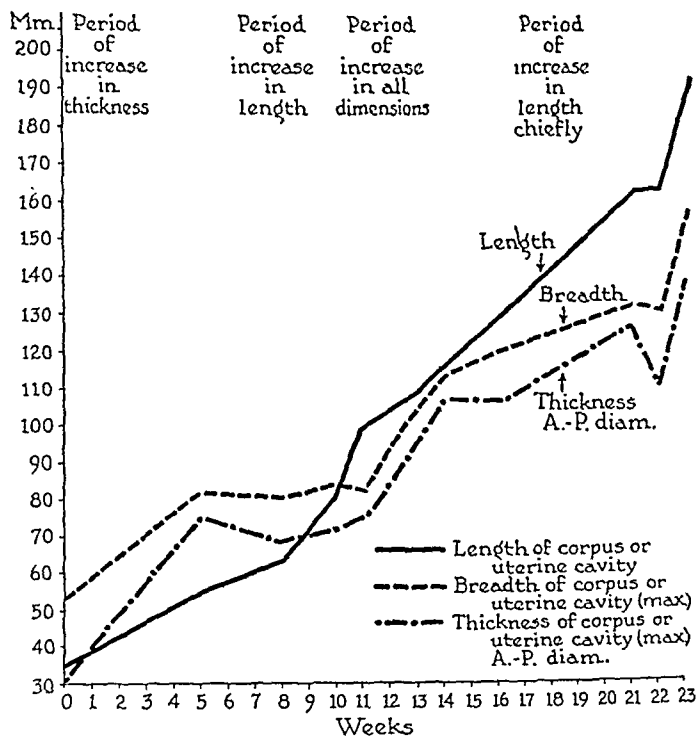


Fig. 6.—Curves constructed from Stieve's data (Table I), which compare favorably with the data in Table II.

3. *Is it reasonable to believe that the entire so-called lower uterine segment which exists prior to and during labor can be the result of growth of the isthmus uteri?* In fact, the answer to this question was the chief reason why we measured 73 frozen sections of the uterus in the various stages of pregnancy. To obtain the data shown in Table II we selected those frozen sections which appeared to be most free from uterine pathology. This, of course, decreased the number of sections available. Measurements of excised specimens found in the literature were also measured and studied.

In answering this question it was necessary to make two assumptions. First, the retraction ring or a definite thickening of the wall marks the junction of the upper and lower segments. Second, if the lower segment develops from the isthmus, then the longitudinal muscle fibers of the

uterus. This is coincident with the unfolding of the isthmus, as indicated by the histologic studies of the mucosa.

It should also be noted (Table II) that the distance between the lower edge of the placenta and the internal os rather suddenly increases between the third and fourth months.

Third, one may expect the unfolding of the isthmus to cause a change in the rate of growth and possibly in the form of the uterine cavity. The ratio of the length of the uterine cavity to its sagittal circumference as shown in Table II may be taken as an indicator of the form of the uterine cavity. By the fourth month, the cavity has assumed the shape which it maintains to term. This may be an indication that the unfolding of the isthmus is completed at this time.

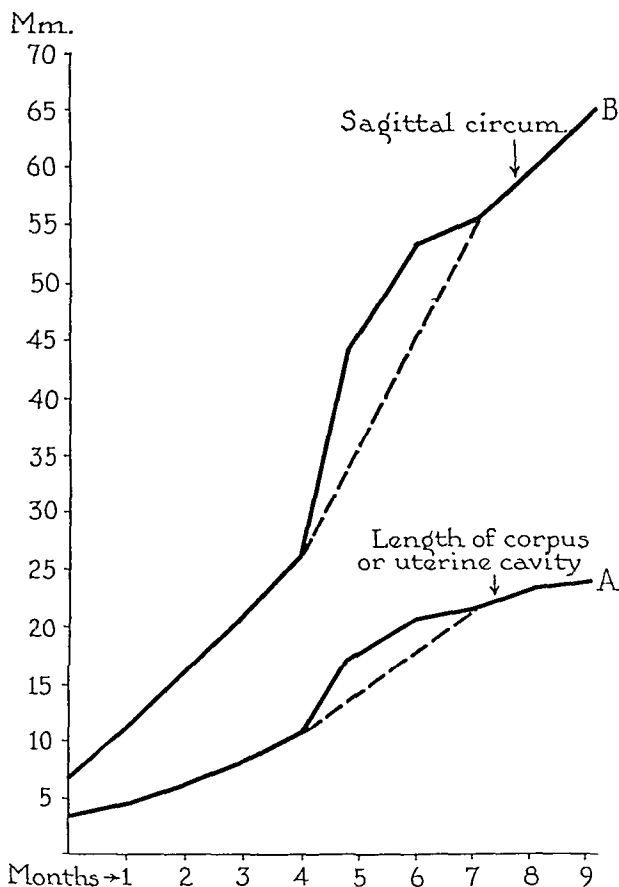


Fig. 5.—Curves of the growth in the length and the sagittal internal circumference of the corpus or general uterine cavity in various stages of pregnancy. Note the marked increase which occurs between the fourth and sixth month. Curves constructed from data (Table II) from frozen sections.

Changes in the rate of growth of the uterine cavity reveal another possibility. A study of Fig. 5 will show that there is a sudden increase in the growth rate during the fourth to sixth months. If one assumes first that the lower uterine segment is made up of the isthmus uteri, and second that the isthmus reaches its final length before it begins to unfold, one can account for this sudden increase in growth rate by an unfolding of the isthmus and its addition to the circumference of the uterine cavity:

1. Average length of lower uterine segment = 7.3 cm.
2. Circumference length of lower uterine segment = 14.6 cm.

TABLE IIA. RATE OF CHANGE IN LENGTH AND SAGITTAL CIRCUMFERENCE OF UTERINE CAVITY

| MONTH                 | LENGTH<br>CM. | SAG.<br>CIRCUM.<br>CM. | A.<br>INCREASE<br>IN<br>LENGTH<br>CM. | B.<br>INCREASE<br>IN<br>CIRCUM.<br>CM. | B. - A.<br>SLOPE<br>OF<br>CURVE |  |
|-----------------------|---------------|------------------------|---------------------------------------|--|---------------------------------|--|
| 0                     | 3.4           | 6.8                    | —                                     | —                                      | —                               |  |
| 0 to 1st              | 4.6           | 10.4                   | 1.2                                   | 3.6                                    | 3.0                             | } 2.95 } 2.87  |
| 1st to 2nd            | 6.2           | 15.3                   | 1.6                                   | 4.9                                    | 3.1                             |  |
| 2nd to 3rd            | 8.2           | 20.8                   | 2.0                                   | 5.5                                    | 2.75                            |  |
| 3rd to 4th            | 10.4          | 26.6                   | 2.2                                   | 5.8                                    | 2.64                            |  |
| 4th to 5th            | 17.1          | 44.0                   | 6.7                                   | 17.4                                   | 2.6                             | } 2.56 } 2.54  |
| 5th to 6th            | 20.9          | 53.5                   | 3.8                                   | 9.5                                    | 2.5                             |  |
| 6th to 7th            | 21.7          | 55.3                   | 0.8                                   | 1.8                                    | 2.3                             |  |
| 7th to 8th            | 23.5          | 60.5                   | 1.8                                   | 5.2                                    | 3.0                             |  |
| 8th to 9th            | 24.6          | 65.0                   | 1.1                                   | 4.5                                    | 4.0                             | } Relation of<br>length to cir-<br>cumference is<br>close to that of<br>a circle |
| 9 mo.,                | 25.3          | 66.7                   | 0.7                                   | 1.5                                    | 2.1                             |  |
| 1st stage<br>of labor |               |                        |                                       |  |                                 |  |

isthmus during pregnancy should increase in length to the same extent as those of the corpus.

The actual measurements reveal that the musculature of the corpus elongates in its sagittal circumference from 6.9 to 8.0 times during pregnancy. The musculature of the isthmus elongates in its sagittal internal surface from 7.3 to 13 times. If one chooses the average circumference of the nongravid corpus (6.9 cm.) and chooses 1.0 cm. as the length of one side of the nongravid isthmus, then the corpus increases in length 7.4 times and the isthmus 7.3 times.

#### CALCULATIONS REGARDING THE SAGITTAL GROWTH OF THE ISTHMUS AND CORPUS UTERI IN PREGNANCY

- A. Average internal sagittal circumference of uterine cavity at term (Table II).  
Average of 9 mo. term and 9 mo. first stage 65.8 cm.
- B. Average internal sagittal circumference contributed by lower uterine segment:
1. Length of lower uterine segment, cesarean section, Marshal and others 7-10 cm.;
  2. Average length of lower uterine segment, frozen section (Table III) 7.3 cm.  
(2 × 7.3) = 14.6 cm.
- C. Average sagittal circumference contributed by corpus (A-B) 51.2 cm.
- D. Average sagittal circumference of uterine cavity in
- |                        |         |
|------------------------|---------|
| Nulliparous (Table II) | 6.3     |
| Multiparous (Table II) | 7.4     |
| Average                | 6.9 cm. |
- E. Increase in sagittal circumference of corpus in pregnancy:
1.  $51.2 \div 6.3$  (Nulli) = 8.0 times.
  2.  $51.2 \div 7.4$  (Multi) = 6.86 times.
  3.  $51.2 \div 6.9$  (Ave.) = 7.4 times.
  4. Using only 9 mo. term or 9 mo., first stage measurements, or both (Table III), to conform with "A" above the average length of one wall of the lower uterine segment is 9.1, or 11.1 (average with cervix) minus 2.5 (average length of cervix), which equals 9.1 cm., or  $2 \times 9.1 = 18.2$ .  
 $65.8 - 18.2 = 47.6$  cm., for the sagittal circumference of corpus.

TABLE II. RESULTS OF CERTAIN MEASUREMENTS MADE ON HUMAN FROZEN SECTIONS.\* 66 SECTIONS WERE MEASURED AS COMPLETELY AS THE SECTION PERMITTED

| STAGE OF PREGNANCY     | NO. OF CASES | EXT. FUND. TO E. O. CM. | INT. LENG. OF CAVITY C CM. | LENG. OF CERVIX CM. | THICK. OF FUND. WALL CM. | LOWER EDGE OF PLACENTA TO I.O. CM. | DIAM. OF PLACENTA CM. | CIRCUM. OF CAVITY CM. | RATIO OF LENGTH TO CIRCUM. OF CAVITY C-D |
|------------------------|--------------|-------------------------|----------------------------|---------------------|--------------------------|------------------------------------|-----------------------|-----------------------|--|
| 1 month                | 6            | 9.0                     | 4.6                        | 3.6                 | 0.8                      | —                                  | —                     | 10.4                  | 44.2                                     |
| 2 months               | 3            | 11.3                    | 6.3                        | 4.0                 | 1.0                      | —                                  | —                     | 15.3                  | 44.2                                     |
| 3 months               | 6            | 12.5                    | 8.2                        | 4.1                 | 1.0                      | 1.3                                | —                     | 20.8                  | 40.0                                     |
| 4 months               | 8            | 15.4                    | 10.4                       | 4.3                 | 0.7                      | 2.8                                | 10.5                  | 26.6                  | 39.1                                     |
| 5 months               | 4            | 21.6                    | 17.1                       | 3.6                 | 0.7                      | 6.8                                | 13.1                  | 44.0                  | 38.8                                     |
| 6 months               | 3            | 24.5                    | 20.9                       | 3.0                 | 0.7                      | 9.0                                | —                     | 53.5                  | 39.0                                     |
| 7 months               | 5            | 25.4                    | 21.7                       | 3.4                 | 0.5                      | 11.1                               | 16.0                  | 55.3                  | 39.2                                     |
| 8 months               | 4            | 26.5                    | 23.5                       | 2.4                 | 0.6                      | 13.2                               | 15.4                  | 60.5                  | 38.8                                     |
| 8 months (early labor) | 3            | 27.3                    | 24.2                       | 1.3                 | 0.8                      | 11.9                               | 17.2                  | 61.9                  | 39.0                                     |
| 9 months               | 5            | 27.7                    | 24.6                       | 2.7                 | 0.7                      | 15.2                               | 17.5                  | 65.2                  | 38.0                                     |
| Labor, 1st Stage       | 8            | 28.1                    | 25.3                       | 2.0                 | 0.7                      | 13.0                               | 17.2                  | 66.7                  | 38.0                                     |
| Labor, 2nd Stage       |              |                         |                            |                     |                          | E. O.                              |                       |                       |  |
| Bumm and Blumreich     |              | --                      | 26.9                       | 2.0                 | —                        | 7.0                                | —                     | 69.6                  | 38.6 Early                               |
| Hillis                 |              | 34.5                    | 30.5                       | 3.2                 | 0.8                      | 15.0                               | 18.0                  | 71.2                  | 42.8 Early                               |
| Braune                 |              | 27.4                    | 26.5                       | 0.1                 | 0.8                      | 15.3                               | 18.0                  | 65.4                  | 40.5 Early                               |
| Canton                 |              | 25.3                    | 22.9                       | 0.6                 | 1.8                      | 11.6                               | 15.0                  | 55.7                  | 41.1 Vertex deep                         |
| Barbour and Webster    |              | 24.0                    | 22.9                       | 0.1                 | 1.1                      | 8.4                                | —                     | 55.9                  | 40.9 Vertex at vulva                     |
| Couvelaire             |              | 22.8                    | 22.0                       | 0.3                 | 0.5                      | 11.7                               | 14.0                  | 51.5                  | 42.7 Vertex at vulva                     |
| Canton                 |              | 17.2                    | 15.6                       | 0.3                 | 1.3                      | —                                  | 10.1                  | 41.6                  | 37.5 Vertex at vulva                     |
| Labor, 3rd Stage       |              | Total Int. Leng.        |                            |                     |                          |                                    |                       | Total Int. Circum.    |  |
| Placenta not separated | 4            | 18.5                    |                            |                     |                          |                                    |                       | 46.3                  | 40.0                                     |
| Placenta separated     | 4            | 17.7                    |                            |                     |                          |                                    |                       | 40.1                  | 44.1                                     |
| 1st day, post partum   | 4            | 18.0                    |                            |                     |                          |                                    |                       | 41.2                  | 43.6                                     |
| 1-5 days, post partum  | 6            | 13.7                    |                            |                     |                          |                                    |                       | 30.5                  | 45.0                                     |
| Nonpregnant Nulli      | 6            | 6.8                     | 3.1                        | Is. 0.5<br>Cx. 2.7  | 0.5                      |                                    |                       | 6.3                   | 50.0                                     |
| Nonpregnant Multi      | 4            | 7.8                     | 3.7                        | Is. 0.7<br>Cx. 2.7  | 0.7                      |                                    |                       | 7.4                   | 50.0                                     |

\*Only those which involved no pathology of uterus or pelvis are included. The sections are sagittal.

TABLE III. AN ANALYSIS OF THOSE CASES SHOWING DEFINITE RETRACTION RINGS OR THICKENING AT JUNCTION OF UPPER AND LOWER SEGMENTS  
(HUMAN FROZEN SECTIONS)§

| OUR<br>CASE | LOCATION OF<br>P.R.R. OR<br>RING |    | P.P.R.*<br>TO<br>E. O. |      | BLAD-<br>DER**<br>FOLD TO<br>E. O.                   | FUNDUS†<br>TO<br>R.R. |      | R.R.‡ TO LEVEL<br>OF SYMPHYSIS<br>VERTICAL |       | R.R. COR-<br>RESPONDS<br>TO FETAL<br>DE-<br>PRESSION | AVERAGE<br>LENGTH<br>OF<br>CERVICAL<br>LIPS | STAGE<br>OF<br>LABOR | NATURE<br>OF<br>RING |
|-------------|----------------------------------|----|------------------------|------|--|-----------------------|------|--|-------|--|---|----------------------|----------------------|
|             | A.                               | P. | A.                     | P.   |  | A.                    | P.   | A.   | P.    |  |   |                      |                      |
| 16          | ×                                | ×  | I.O.                   | I.O. | 7.0 I.O.   | 28.7                  | 18.3 | 0  | 8.5   | ---  | ?   | 9, Term              | Thickening           |
| 17          | 0                                | ×  | 12.0                   | 11.2 | 3.5 I.O.   | 30.2                  | --   | --   | --    | ---  | ?   | 9, Term              | Thickening           |
| 19          | ×                                | 0  | 12.4                   | --   | 6.0  | 20.9                  | --   | --   | --    | ---  | 2.5   | 9, Term              | Thickening           |
| 21a         | ×                                | ×  | 14.2                   | 10.6 | 5.2  | 23.4                  | 23.7 | +11.8                                      | --    | ---  | --  | 9, Term              | Thickening           |
| 24          | 0                                | ×  | 9.5                    | 11.1 | 9.8  | --                    | 18.1 | + 1.0                                      | + 8.1 | Yes  | 2.1   | 8, Term I            | Definite             |
| 31          | ×                                | ×  | 10.7                   | 13.7 | 7.5  | 26.9                  | 23.4 | 0  | + 7.0 | Yes  | 2.6   | 9, Term I            | Definite             |
| 33          | ×                                | ×  | 12.0                   | 15.6 | ?  | 21.5                  | 14.9 | + 0.8                                      | +10.0 | Yes  | 2.4   | 9, Term I            | Definite             |
| 40          | ×                                | ×  | 9.5                    | 7.9  | 2.2  | 26.3                  | 28.8 | + 9.6                                      | + 9.2 | Leg down   | 0   | 9, Term I            | Definite             |
| 41          | ×                                | ×  | 6.4                    | 11.9 | 6.8  | 36.8                  | 18.5 | + 3.0                                      | 10.6  | Yes  | 2.0   | Term, II             | Definite             |
| 42          | ×                                | ×  | 10.8                   | 10.6 | 7.6  | 20.7                  | 23.7 | + 3.0                                      | + 9.7 | Yes  | 0.1   | Term, II             | Definite             |
| 43          | ×                                | ×  | 8.4                    | 7.6  | 4.1  | 23.1                  | 18.8 | + 4.0                                      | + 9.0 | Yes  | 0.1   | Term, II             | Definite             |
| 44          | ×                                | ×  | 8.5                    | 5.8  | 6.8  | 24.1                  | 18.6 | + 2.0                                      | + 8.2 | Yes  | 0.7   | Term, II             | Definite             |
| 46          | ×                                | ×  | 6.4                    | 4.3  | 4.8  | 17.3                  | 17.5 | 4.2  | 7.6   | Yes  | --  | Term, II             | Definite             |
| 47          | ×                                | ×  | 3.0                    | 4.3  | ?  | 20.2                  | 14.7 | + 2.2                                      | + 6.8 | Yes  | 0.6   | Term, II             | Definite             |
| 48          | ×                                | ×  | 8.3                    | 5.3  | 3.0  | 16.3                  | 14.7 | + 0.7                                      | - 0.1 | ---  | 2.4   | Term, III            | Definite             |
| 53          | ×                                | ×  | 9.0                    | 6.6  | ?  | 11.3                  | 11.2 | --   | --    | ---  | ?   | Term, III            | Definite             |
| 55          | ×                                | ×  | 7.1                    | 3.0  | 6.4  | 13.9                  | 14.2 | - 2.7                                      | - 0.9 | ---  | 1.3   | P.P.                 | Definite             |
| 56          | ×                                | ×  | 9.0                    | 4.8  | 7.3  | 12.3                  | 20.7 | + 4.4                                      | + 5.2 | ---  | 2.0   | P.P.                 | Definite             |
| Ave.        |                                  |    | 9.2                    | 8.4  | 5.9  |                       |      | + 3.7                                      |       |  | 1.5   |                      |                      |
| Ave.        |                                  |    | 8.8                    |      | Ave. length of l.u.s. = 8.8 - 1.5 (cervix) = 7.3 cm. |                       |      |  |       |  |   |                      |                      |

\*Hillis case not included.

\*\*The measurements represent the distance measured circumferentially along the internal curvature of the uterus.

†Ant. P.R.R. is above level of symphysis in all cases including those from 8 months to end of second stage. Total cases, 18; average vertical distance above level of symphysis is 4.0 cm.; range = +0.3 to +11.8 cm.

‡Note that on the average the bladder fold of the peritoneum is 3.3 cm. below the P.R.R. This checks well with Marshall (1, p. 45). The bladder fold is below the P.R.R., but the very firm attachment of peritoneum to uterus is generally above (2 to 3 cm.) the P.R.R.  
§P.R.R., Physiologic retraction ring; A., anterior; P., posterior; l.u.s., lower uterine segment.

$47.6 \div 6.9$  (average circumference, nongravid, uterine cavity) = 6.9 times.

F. Increase in sagittal length of corpus in pregnancy ranges from 6.9 to 8.0 times.

G. The increase of the length of the isthmus in pregnancy depends on the length accepted for the nongravid isthmus.

1. The maximum length of one wall is 1.0 cm.;

2. The minimum length of one wall is 0.45 cm.;

3. The average length of one wall is 0.7 cm., or

Average total length is  $2 \times 0.7 = 1.4$  cm., on the basis of maximum length; the total length is 2.0 cm.

a.  $14.6$  (see B 2 above)  $\div 2.0 = 7.3$  times.

b.  $14.6 \div 0.9 = 16.2$  times.

c.  $14.6 \div 1.4 = 10.4$  times.

d.  $18.2$  (see E 4 above)  $\div 1.4 = 13.0$  times.

e.  $18.2$  (see E 4 above)  $\div 2.0 = 9.1$  times.

H. Increase in sagittal length of isthmus in pregnancy ranges from 7.3 to 13.0 times, omitting the minimum figure for the length of the isthmus.

The correlation between the extent of growth in length of the isthmus and corpus is striking. This is particularly true when one recalls that before the physiologic retraction ring becomes definitely evident, some increase in the length of the fibers of the isthmus and decrease in the length of the fibers of the corpus may have occurred. Keeping this in mind, it is reasonable to believe that all of the so-called lower segment, exclusive of that contributed by the true cervix in labor, develops from the isthmus. The only way to settle the question would be to place some nonabsorbable material at the level of the retraction ring in labor, and then determine its position in the fully involuted uterus.

### III. CERTAIN OBSERVATIONS RESULTING FROM A STUDY OF FROZEN SECTIONS OF THE HUMAN UTERUS

In the preceding study it was necessary to identify the "retraction ring" or the junction of the isthmus and corpus as accurately as possible. This caused us to make measurements which are of interest in relation to the lower segment cesarean operation and to the problem of constriction ring dystocia.

*The Relation of the Lower Edge of the Placenta to the Retraction Ring and the Obstetric Internal Os.*—In the monkey the lower edge of the placenta, as a rule, was a good indication of the site of the physiologic retraction ring in labor. This was not found to be so true in the human being.

In the term uterus (9 mo.), the lower edge of the placenta was located on the average 15.2 cm. circumferentially above the obstetric internal os (Table II). The retraction ring was located on the average 9.1 cm. circumferentially above the obstetric internal os. Or, the lower edge of the placenta was located on the average 3.1 cm. above the retraction ring. In the ninth month, first stage specimens, the lower edge of the placenta was located on the average 2.1 cm. ( $13.0 - 9.1 = 2.1$  cm.) above the retraction ring.

*The Relation of the Retraction Ring to the Peritoneal Bladder Fold.*—The average circumferential distance from the bladder fold to the external cervical os was 5.9 cm. (Table III). The average circum-

second stage of labor were located above the horizontal plane of the superior border of the symphysis. In 13 cases in which the ring was located anteriorly, the average vertical distance from the symphysis to the ring was 3.7 cm., the range being -2.7 (one case) to +11.8 cm. (Table III).

*The Thickness of the Uterine Musculature or Wall at Various Levels Before and During Labor.*—The thickness of the uterine wall was measured at the points indicated in Table V. An analysis of the data reveals

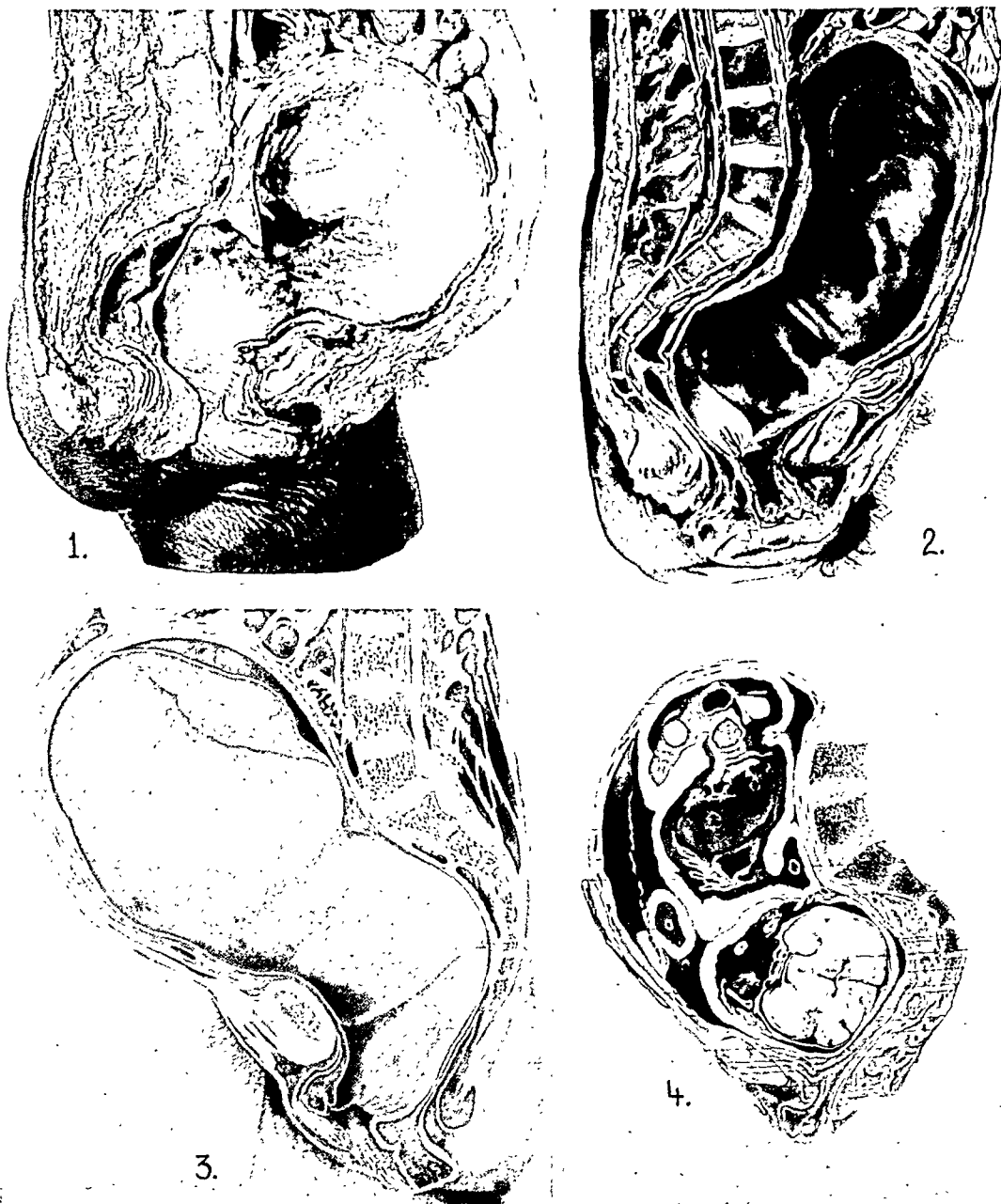


Fig. 8.—Frozen sections illustrating the variability in retraction rings in the absence of disproportion. Section 1 is from Canton; Section 2 is from Canton; Section 3 is from Braune; and Section 4 is from Barbour. Barbour's section was in the first stage. The others are second stage.





TABLE V. THICKNESS OF WALL OF UTERUS AT VARIOUS LEVELS BEFORE AND DURING LABOR  
(HUMAN FROZEN SECTIONS)†

| STAGE      | NO. OF CASES | MIDWAY BETWEEN CERVIX AND P.R.R. OR THICKENING |                 | JUNCTION OF U.U.S. AND L.U.S. |                    | MIDCORPUS        |                   | TOP OF FUNDUS    | AVERAGE L.U.S. WITHOUT CERVIX CM. |
|------------|--------------|--|-----------------|-------------------------------|--------------------|------------------|-------------------|------------------|-----------------------------------|
|            |              | ANT. MM.                                       | POST. MM.       | ANT. MM.                      | POST. MM.          | ANT. MM.         | POST. MM.         |                  |                                   |
| 9 mo. Term | 6            | 5.1<br>2.5-7.0                                 | 5.7<br>2.0-10.0 | 7.0<br>4.5-8.5                | 7.8<br>5.5-11.0    | 7.0<br>3.5-10.0  | 7.4<br>5.0-9.0    | 7.0<br>5.0-8.0   | 9.1<br>6.8-11.7 Ave. Range        |
| 8 mo. 1st  | 3            | 2.0<br>1.5-2.5                                 | 4.4<br>3.5-6.0  | 4.3<br>4.0-5.0                | 5.8<br>5.0-7.0     | 7.0<br>5.5-9.5   | 7.8<br>5.5-10.0   | 7.8<br>5.5-10.0  | Ave. Range                        |
| 9 mo. 1st  | 9            | 3.2<br>1.0-5.0                                 | 4.2<br>2.5-6.5  | 5.6<br>4.5-7.0                | 5.6<br>4.0-8.0     | 7.4<br>6.0-11.0  | 6.2‡<br>2.5-8.0   | 7.4<br>2.5-23.0  | 9.3<br>7.9-13.2 Ave. Range        |
| 9 mo. 2nd  | 7            | 3.5<br>2.5-6.0                                 | 4.6<br>3.0-8.0  | 6.0<br>4.0-8.0                | 14.5*<br>5.0-36.0* | 10.3<br>7.0-18.0 | 10.7<br>6.5-22.0* | 10.3<br>5.0-15.0 | 6.6<br>3.0-9.9 Ave. Range         |

\*Due to a very thick R.R. and retraction of posterior uterine wall; may have been a Bandl's ring, though there was no disproportion and the l.u.s. was not thin, but retracted markedly longitudinally.

‡Due to excessive thinning anteriorly and thickening posteriorly in one specimen by Leopold.

Note: During the first stage, the average length of the l.u.s. increases only slightly, if any; however, the l.u.s. becomes definitely thinner, which must be due to distention or an horizontal increase in length. During the second stage, the average length of the l.u.s. decreases definitely and the corpus becomes definitely thicker.

†U.U.S., upper uterine segment; L.U.S., lower uterine segment.

TABLE IV. SUMMARY OF DEFINITE RETRACTION OR "CONSTRICTION RINGS"

|  | PER CENT |
|--|----------|
| I. Of 73 cases studied, physiological retraction ring, or a definite retraction ring was present in 38, or | 52.0     |
| Definite ring, present in 14 cases   | 19.2     |
| Thickening only, present in 24 cases   | 33.0     |
| II. Of 48 cases during labor and up to fourth day post partum:   |          |
| Ring present in 14 cases.  | 29.9     |
| III. Of 14 definite rings:   |          |
| 3 occurred in first stage of 17 cases  | 17.6     |
| 1 occurred in Braxton Hicks' Version of 3 cases  | 33.3     |
| 6 occurred in second stage of 8 cases  | 75.0     |
| 2 occurred in third stage of 8 cases   | 25.0     |
| 2 occurred in post partum of 11 cases  | 18.2     |

(The unpublished case of Dr. Hillis is included.) Of the 10 rings found in the first and second stages, 9, or 90 per cent, correspond to fetal depressions. The other one occurred in a Braxton Hicks' version.

that on the average during the first stage of labor the length of the lower segment increases only slightly, if any. The lower segment, however, becomes definitely thinner. This must be due chiefly to an horizontal increase in the length of the circular musculature. During the second stage, the average length of the lower segment definitely decreases, i.e., from 9.1 to 6.6 cm.

On reviewing and measuring the thickness of the uterine wall in labor, one is amazed by the variability particularly in the retraction of the corpus, as revealed by the frozen section method.

*Changes in the Position and Length of the Cervical Lips.*—In the monkey in labor, it was found that the cervical lips during the second stage of labor (frozen sections) retracted about the presenting part to the level, or usually above the level of the superior border of the symphysis.<sup>118</sup> The data from the frozen sections of the human uterus are presented in Table VI. Unfortunately in many cases the section did not pass through the cervical canal. For this reason some of the sections are of no value for detailed mensuration.

The data obtained (Table VI) indicate that from the eighth month of pregnancy to the beginning of the second stage of labor the cervical lips tend to sink in relation to the symphysis. During the second stage, they are definitely elevated and even the anterior lip in some instances (2 of 7) may rise slightly above the symphysis. This occurs in the absence of known disproportion. This is particularly true of the posterior lip (see Fig. 7).

The excursion of the cervical lips during labor in the living subject is best studied by placing radiopaque clips on the cervical lips. This method, which is being employed by Caldwell and Stillman,<sup>5</sup> should yield precise information. Their preliminary results indicate that the cervical lips in the human being during the second stage of labor retract to a higher level in labor than is generally believed.

The frozen sections reveal that the extent to which the cervical lip is retracted into the lower segment in labor is subject to wide variation. In some cases only a lip 2 mm. long hangs below the level of the fornix; in other cases as much as 3.4 cm. In the latter case it appears as if no retraction of the cervix into the lower segment has occurred.

f. To obtain direct evidence, it would seem to be necessary to place some nonabsorbable material in the musculature at the site of the retraction ring in labor and then determine the site of the material in the fully involuted uterus.

3. Data obtained from the mensuration of frozen sections of the human uterus have been analyzed in relation to the location and variability of the physiologic retraction ring and the position and dilatation of the cervical lip during labor.

NOTE: It should be stated that all the data on which the averaged values in the tables are based cannot be published in a short article. Dr. D. N. Danforth and I hope to publish a monograph including photographs of all frozen sections and the data upon which the averaged values are based.

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TABLE VI. SHOWING LEVEL OF CERVICAL LIPS AND EXTERNAL HEIGHT OF FUNDUS IN RELATION TO THE HORIZONTAL PLANE OF THE UPPER BORDER OF THE SYMPHYSIS (HUMAN FROZEN SECTIONS)

| STAGE          | NO.<br>OF<br>CASES | CERVICAL LIPS AS RELATED TO LEVEL<br>OF SYMPHYSIS* |              |           |              | HEIGHT OF FUNDUS<br>ABOVE PLANE OF<br>SYMPHYSIS |              |
|----------------|--------------------|--|--------------|-----------|--------------|---|--------------|
|                |                    | ANTERIOR   |              | POSTERIOR |              | AVE.  | RANGE        |
|                |                    | AVE.   | RANGE        | AVE.      | RANGE        |   |              |
| 7 mo.          | 4                  | -2.8   | -1.6 to -4.1 | -2.8      | -1.5 to -4.1 | 20.3  | 18.1 to 24.8 |
| 8 mo.          | 4                  | -0.6   | -1.0 to +0.2 | 0         | -0.6 to +0.7 | 22.9  | 18.9 to 25.9 |
| 9 mo.          | 4                  | -2.2   | -1.5 to -3.7 | -1.2      | 0 to -3.7    | 23.1  | 20.3 to 26.7 |
| 8 mo. I        | 4                  | -0.8   | -2.0 to 0    | +0.6      | -1.0 to +2.0 | 23.2  | 19.4 to 25.8 |
| 9 mo. I        | 6                  | -3.8   | -5.7 to -0.6 | -2.8      | -5.0 to 0    | 23.8  | 17.9 to 32.5 |
| 9 mo. II       | 7                  | -1.3   | -3.8 to +0.7 | +3.8      | +0.3 to +7.4 | 22.4  | 16.7 to 25.5 |
| 9 mo. III      | 3                  | -5.0   | -1.4 to -8.0 | -0.5      | -4.6 to +2.5 | 14.1  | 12.6 to 17.6 |
| Post<br>partum | 8                  | -3.0   | -6.5 to +1.4 | -2.3      | -5.6 to +1.4 | 12.7  | 7.8 to 17.6  |

\* (-) = below level of symphysis; (+) = above; (0) = at level.

Note: According to the data, from eight months to, and including, the first stage of labor the cervical lips tend to sink in the pelvis, but during the second stage they are definitely elevated to sink again at the third stage.

### SUMMARY

1. A structural, as well as a comparative anatomic and physiologic background, exists for the mode of travel of the wave of uterine contraction in the primate uterus.

2. The evidence pertaining to the growth and unfolding or inclusion of the isthmus uteri into the general uterine cavity to form the so-called lower uterine segment may be summarized as follows:

a. Histologically the isthmus uteri increases from 2 to 3 times in length during the first three months of pregnancy and then unfolds and is included in the general uterine cavity. No evidence contrary to this observation in the human being could be found. Histologic and gross anatomic observations in the monkey lend substantial confirmation.

b. The muscular fasciculi of the isthmus in pregnancy assume a more longitudinal or steeper course, but the architecture of the true cervix and corpus is not significantly modified. There is no contrary evidence; yet, one should like to have confirmation of Goerttler's observations.

c. The membranes are relatively loosely attached to the lower segment and the mucosa of the lower segment differs histologically from that of the upper segment. This evidence is not substantial in that no definite line of demarcation between the two segments can be detected.

d. The changes in the form of the uterus in pregnancy are compatible with and suggest that some event happens between the third and fourth month of pregnancy which contributes (a) to a definite change in the breadth and thickness of the uterine cavity, (b) to a greater increase in vertical length in relation to the increase in the sagittal circumference of the cavity, and (c) to a rather sudden increase in the average distance of the lower edge of the placenta from the internal os (Table II).

e. Using the "retraction ring" as the point of junction between the isthmus and corpus in late pregnancy and labor, it was found that the muscular fasciculi undergo approximately equal increases in longitudinal length in pregnancy. Or, it was found reasonable to conclude that an isthmus only 1 cm. long in the nongravid state may hypertrophy until it is 7 to 10 cm. in length at term.

## MATERIAL

So far 61 women from 26 to 44 years of age have helped in this study. They had had from 2 to 15 pregnancies each. There had been an average of 7.3 previous pregnancies in those cases in which normal ova were obtained, an average of 6.8 pregnancies each in cases in which abnormal ova were recovered, and an average of 4.8 previous pregnancies per patient in the 48 cases in which young embryos were not found.

Of the 12 conceptuses recovered in the course of this investigation, 7 are considered to be normal. One lacks the embryo, so it may be said to be congenitally destined for abortion, and four others are probably so. The only endometrial deviation from normal was seen in the one case, Be-7771, which is minus the embryo. This ovum is situated in a polypoid bit of mucosa (Fig. 3).

Two of the normal ova, Si-7699 and Al-7700, were reported briefly to the American Association of Anatomists in 1939, and the material pertaining to Al-7700 was published as an abstract in the *Anatomical Record*.<sup>1</sup> Later both these specimens were described in detail in the *Contributions to Embryology* of the Carnegie Institution of Washington.<sup>2</sup> Five of the normal embryos (including the two mentioned above) and four of the pathologic ones were discussed before the American Society for Experimental Pathology in April, 1942.<sup>3</sup> In a paper read before the American Association of Anatomists, also in the spring of 1942, Re-7950 and Si-7699 were compared with regard to their respective implantation sites.<sup>4</sup>

The present paper utilizes three additional ova: one abnormal, Sm-8000, and two normal, Mu-8020 (Fig. 1) and Wi-8004 (Fig. 2). The latter two specimens, estimated to be between 7 and 8, and between 9 and 10 days old, respectively, are, as far as we know, the youngest human embryos ever seen and are now reported for the first time. The next three normal ova in the order of age, dated 11.5, 12.0, and 12.5 days old (mean values), are represented in Figs. 3, 4, and 5, respectively.

The structural details of the specimens not already described will in time appear in the *Contributions to Embryology* of the Carnegie Institution of Washington. We merely wish to mention a few of the clinical lessons derived from our studies thus far.

The following subjects are considered:

1. The probable time of ovulation as evidenced by embryo age and endometrial histology.
2. The time of nidation.
3. The location of embedment.
4. The frequency of abnormal ova.

#### 1. THE PROBABLE TIME OF OVULATION AS EVIDENCED BY EMBRYO AGE AND ENDOMETRIAL HISTOLOGY

The ages of 11 embryos have been tentatively estimated by Drs. Streeter and Heuser by comparing their development with that of monkey conceptuses of known ovulation ages. The twelfth specimen, Be-7771, is undatable, since it lacks an embryo.

How long a time elapses between ovulation and fertilization? It seems likely that for prolonged orderly development to occur after the

## SOME ASPECTS OF EARLY HUMAN DEVELOPMENT\*

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TO FURTHER a comprehensive study of the factors of human reproduction, we have started, at the Free Hospital for Women, the systematic collection of human ova. Among several hundred eggs obtained from follicles, we have recovered two in the first maturation division. We have also isolated one perfect unfertilized tubal ovum. From uteri removed at operation we have recovered twelve very young human conceptuses with which this report deals. Together with the tubal ovum, these specimens have been added to the collection of primate ova in the Department of Embryology of the Carnegie Institution of Washington.† Here they are utilized by Doctors George W. Corner, George L. Streeter, and Chester Heuser in their study of human embryology. To these investigators and their associates we owe the careful sectioning and photographing of the specimens. We are also grateful for their help in the basic interpretations on which this paper rests.

The heavy clinical load of the Free Hospital for Women has been admirably adapted to our purpose. Patients seen in the Out-Patient Department who require surgical relief for conditions not immediately harmful must await hospitalization usually for several months. From women who are put on the list for operation by the examining surgeons in the Out-Patient Department we select those to whom the following statements apply:

1. They are incapacitated by symptoms caused by gross uterine displacement or minor uterine pathology, which can best be relieved by hysterectomy.
2. Their menstrual habit is such as to indicate probable regular ovulation.
3. They are living with their husbands and are willing and intelligent enough to cooperate.

The selected patients are asked to report each menstrual period during the months of waiting for admission and to record the dates of coitus during the cycle in which operation is to take place. In some of the more recent cases urine for assay of hormones has also been collected prior to operation.

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†The accession numbers of the Carnegie Institution of Washington are used to designate the specimens discussed in this report.

anticipated period. For other reasons, we believe this is not so. Two of our cases are better controlled than the others and give more dependable information on this subject. In each of these there was but a single insemination. Ovulation could not have preceded coitus by many hours. In Mu-8020, coitus took place late on the sixteenth day of the cycle. At laparotomy performed on the twenty-fourth day, the endometrium showed that there were still six days to go before a menstrual predecidua would probably be developed; i.e., it is apparent that, in the absence of pregnancy, menstruation would have occurred on the thirtieth day of the cycle. The conceptus obtained is considered to be seven to eight days old. Hence ovulation in this well-controlled case took place

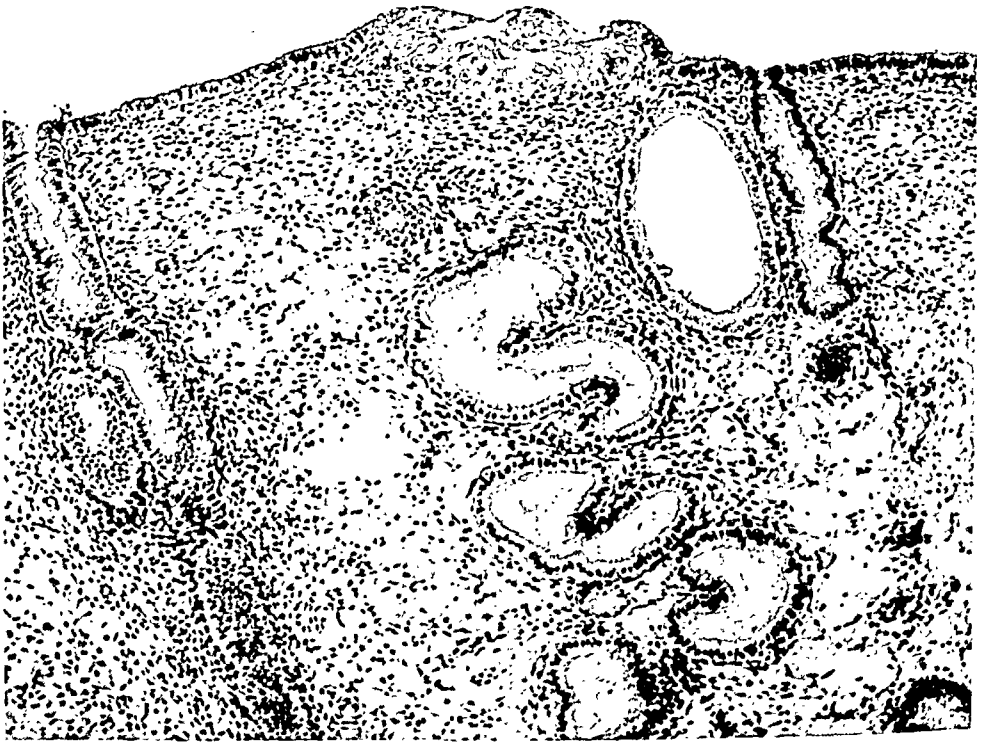


Fig. 1.—Mu-8020. A 7.5-day human ovum implanted on physiologically edematous twenty-two-day secretory endometrium. At its site of attachment to the endometrium, the ovum shows a thick proliferation of its trophoblast which is mostly of the syncytial type. The embryo is represented by the rounded mass of cells just above the trophoblastic mass and beneath the thin membranous portion of the collapsed blastocyst wall. The surface epithelium of the endometrium is defective at the site of implantation but is undergoing proliferative repair at the margin of the defect. Hematoxylin and eosin.  $\times 100$ . Figures are arranged in the order of ascending age of the ova.

fourteen to thirteen days  $[(8 \text{ to } 7) + 6]$  before anticipated menstruation, and between days sixteen and seventeen of the cycle. In Case Al-7700, operation was performed on the twenty-ninth day, but the endometrium showed that a menstrual predecidua would not have developed until two days later. The conceptus is considered to be twelve to thirteen days old. Ovulation therefore is judged to have occurred fifteen to fourteen days  $[(13 \text{ to } 12) + 2]$  before anticipated menstruation, and between days sixteen and seventeen of the cycle.

Hence it appears in these two cases that ovulation takes place about fourteen days before menstruation. In a twenty-seven-day cycle (with

first maturation division, the regulating influence of the male pronucleus must be added within a short time, for it has been found, both in human beings and in lower mammals, that, although segmentation may occur in vivo in unfertilized ova,<sup>5-8</sup> atresia soon follows. We have noted abnormal cleavage in human ovarian eggs during the first twenty-four hours of culture in vitro. On the basis of present evidence, it seems likely that no more than one day intervenes between ovulation and fertilization. This time interval may be taken then as the possible error in age of embryo when it is considered the same as ovulatory age. The ovulation ages recorded in Table I range from between 7 and 8 to between 16 and 17 days or, expressed in terms of mean values, from 7.5 to 16.5 days.

TABLE I. TIME OF OVULATION IN CYCLE AS INDICATED BY AGE OF EMBRYO AND CONDITION OF ENDOMETRIUM ON DAY OF OPERATION

| CASE*   | MEAN ESTIMATED AGE OF OVUM (DAYS) | ESTIMATED INTERVAL BETWEEN OPERATION AND NEXT CATAMENIA AS JUDGED BY CONDITION OF ENDOMETRIUM (DAYS) | INTERVAL BETWEEN ESTIMATED OVULATION AND ANTICIPATED MENSTRUATION (DAYS) | DAY OF CYCLE ON WHICH OPERATION TOOK PLACE | ESTIMATED PREOVULATORY INTERVAL (DAYS) |
|---------|-----------------------------------|--|--|--|--|
| Mu-8020 | 7.5                               | 6  | 13.5   | 24   | 16.5                                   |
| Wi-8004 | 9.5                               | 2  | 11.5   | 25   | 15.5                                   |
| Si-7699 | 11.5                              | 3  | 14.5   | 25   | 13.5                                   |
| Tr-7770 | 11.5?                             | 3  | 14.5?  | 31   | 19.5?                                  |
| Er-7850 | 11.5?                             | 3  | 14.5?  | 31   | 19.5?                                  |
| Sm-8000 | 11.5?                             | 3  | 14.5?  | 28   | 16.5?                                  |
| Re-7950 | 12.0                              | 5  | 17.0   | 26   | 14.0                                   |
| Al-7700 | 12.5                              | 2  | 14.5   | 29   | 16.5                                   |
| Br-7800 | 13.0?                             | 2  | 15.0?  | 32   | 19.0?                                  |
| Ru-7801 | 13.5                              | 2  | 15.5   | 28   | 14.5                                   |
| Bu-7802 | 16.5                              | 0  | 16.5   | 33   | 16.5                                   |

\*Ovum Be-No. 7771 is not included in this table since, due to the absence of the embryo, its age could not be estimated.

?Indicates abnormal specimen whose age could not be estimated as accurately as in the cases of normal ova.

Except in the immediate proximity to the embryo, the endometrium, barring unusually persistent edema, seems unaffected by the pregnancy. The third column in Table I shows the estimated time in days needed in each case after the day of operation for those histologic changes to ensue which normally take place in the endometrium before menstruation is begun in a fully developed predecidua. If this stated number of days in each case is added to the age of conceptus, we derive an idea of the time interval by which ovulation preceded anticipated menstruation. This time interval ranges approximately from 11.5 to 17.0 days (Column 4). If now the estimated mean age of the conceptus is subtracted from the cycle day on which operation was performed (Column 5), we see that ovulation took place from days 13.5 to 19.5 of the cycle (Column 6). The cases in which the interval is more than 16.5 days are, however, those of abnormal ova in which the assigned ages may be less accurate than in the normal ones.

The impression might be gained from these figures that ovulation occurs in the middle of the cycle and that it is as accurately placed by reckoning from the onset of the last menstrual flow as from the next



vesicle consists only of the thin shell of the blastocyst itself and a small grouping of cells which, together with the fewer and more primitive "formative" cells, make up the embryonic pole. It is beneath this area that nidation occurs. The trophoblastic nuclei of the auxiliary cells promptly become distinguishable from the formative cells, multiply, and form an invasive syncytium. We have as yet seen no free human blastocyst. In our youngest ovum, Mu-8020 (Fig. 1), syncytium and signs of early lacunae are easily discernible. The number and size of the formative cells in the embryonic disk, and the integrity of the

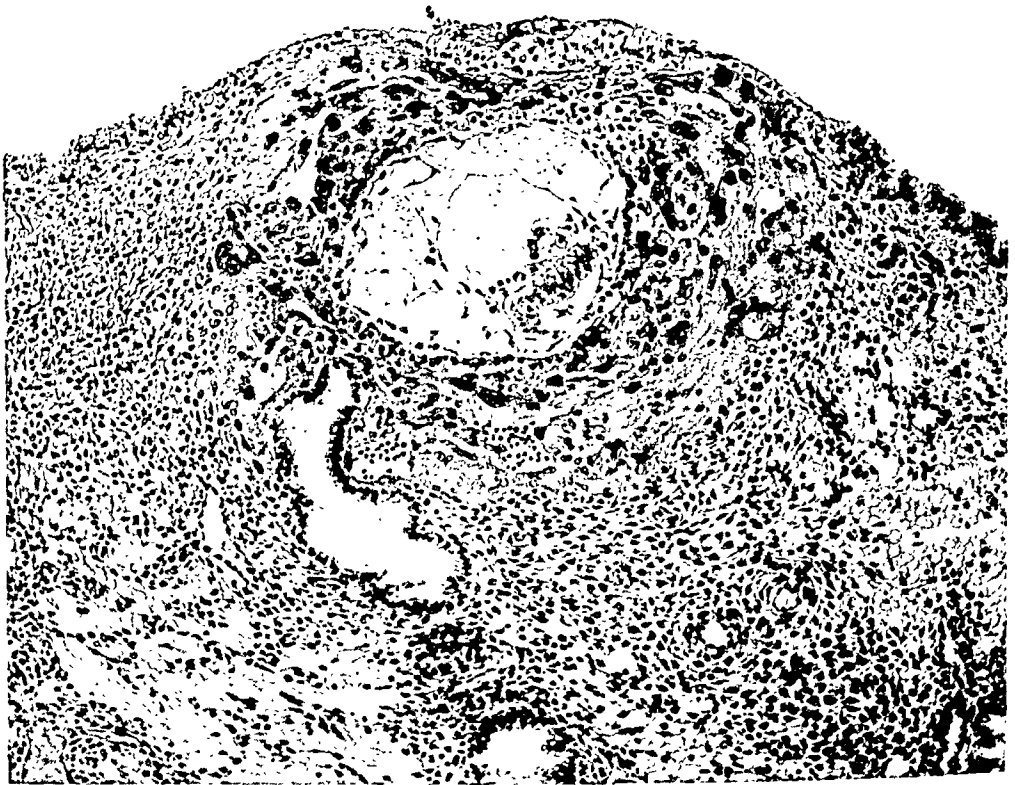


Fig. 3.—Si-7699. An 11.5-day human ovum embedded in twenty-five-day secretory endometrium. The endometrial epithelium has completely regenerated over the ovum, although some coagulum from a near-by defect is apparent on the surface. Within the outer syncytiotrophoblast is an intercommunicating lacunar network containing some maternal blood. The inner cytotrophoblastic layer of the chorion is beginning to develop. The bilaminar germ disk (embryo) is seen toward "4 o'clock," with its amniotic cavity below and its exocoelomic cavity above. There is a suggestion of early decidua about the ovum and the moderately prominent spiral arteriole, with surrounding predecidua in the lower right corner. Hematoxylin and eosin.  $\times 100$ .

amniotic cavity, together with the mass of the whole ovum and the degree of development of the trophoblast, indicate that the conceptus is seven to eight days old. Furthermore it should be noted that the single coitus in this case preceded operation by 7.5 days. Embedment has barely begun, yet the trophoblastic growth must have taken a considerable time, possibly as long as 48 hours, to be accomplished. This would place nidation five to six days after ovulation; i.e., on the nineteenth to the twentieth day of a twenty-seven-day cycle.

Our next specimen in the order of age is that of Wi-8004 (Fig. 2). This was almost completely submerged in the endometrium, yet its histology indicates that it is only nine to ten days old. Judging from

menstruation on the twenty-eighth day) ovulation takes place not only about the fourteenth day ( $14 \pm 2$ ) before the beginning of catamenia, but also in the middle of the cycle. When the cycle is longer than twenty-seven days, as in the two cases mentioned above, ovulation still takes place about the fourteenth day before the first day of flow, but in these cases not in the middle of the cycle. The postovulatory period approaches a constant; the preovulatory phase is of variable length.



Fig. 2.—Wi-8004. A 9.5-day human ovum implanted within the surface of twenty-six-day secretory endometrium. The defective endometrial epithelium has been partially repaired and is in the process of closing the defect created by the implanting ovum. The thick syncytiotrophoblastic plate now contains numerous coalescing lacunae for the reception of maternal blood. Some syncytiotrophoblast has formed on the abembryonic wall of the ovum, due to contact with endometrium. The embryo, a bilaminar germ disk with beginning amniotic cavity below, is composed of a thick plate of ectoderm and a thin plate of primitive endoderm. The cavity within the ovum (future chorionic cavity) contains artifactual blood. Hematoxylin and eosin.  $\times 100$ .

This is a conclusion which we draw not from the small number of conceptuses which we have obtained, but from much more extensive studies of the endometrium as it reflects changing endocrine activity of the ovary. The values in Column 4 of Table I do not vary significantly from the figure  $14 \pm 2$ . Difficult as it is to determine just how long progesterin has been acting on an endometrium, it is even more difficult to determine the exact age of an embryo. The fact that the figures in Column 4 of Table I were derived from estimates in regard to both these factors may account for the minor deviations noted.

## 2. THE TIME OF NIDATION

Heuser and Streeter<sup>9</sup> have shown in the monkey that when contact is made with the endometrium, the trophoblastic tissue of the tiny